Guidelines for the Management of

Nausea and Vomiting in Cancer Patients

104-05531/

Guidelines for the Management of Nausea and Vomiting In Cancer Patients

Management of chemotherapy-induced nausea and vomiting includes treatment strategies for both acute (within 24 hours of chemotherapy administration) and delayed (>24 hours after chemotherapy) emesis.

To plan the initial antiemetic treatment for adult cancer patients, the clinician should assess the chemotherapy regimen to be given (Assessment tools- Page 2). Based on the chemotherapy agent with the highest potential to cause nausea and vomiting (emetogenic potential), appropriate antiemetic agents are selected to manage the acute emesis and delayed emesis (see Page 4 for Adults or Page 6 for Pediatric Patients). These are prescribed along with the chemotherapy. Some new agents pending approval in Canada, with superior antiemetic management outcomes, are included in the options for consideration.

Some agents may be ordered as take-home prescriptions, for dispensing by the patient's community pharmacy. Clinicians must keep in mind the costs of these prescription medications and the patient's ability to pay for these drugs (including co-payments of prescription insurance and uninsured patients).

With each cycle of chemotherapy, nausea and vomiting are assessed, using the Common Toxicity Criteria (or the Graphic Rating Scale) for screening and outcome assessment (see Page 8). Attention must focus on both the present circumstances (i.e. how the patient feels right now) and the historic experience since the last chemotherapy treatment (i.e. worst feelings or emesis after the last treatment). If a patient has experienced an unacceptable level of nausea (>2) or vomiting (>1), and this experience has not been influenced by some other causal factor, the antiemetic prevention strategy should be reconsidered, and, if necessary, altered (see Ongoing Antiemetic Treatment for adults- page 5).

Effective management of acute and delayed nausea and vomiting is crucial to prevention of anticipatory nausea and vomiting. In addition to pharmacologic antiemetic agents, other drugs (such as benzodiazepines) and non-pharmacologic methods (such as muscle relaxation, distraction or music therapy) can modify the patient experience and reduce morbidity and anxiety from nausea and vomiting experiences(s).

Cancer patients may also experience chronic nausea or vomiting not related to treatment. Careful assessment for reversible underlying causes, and a simple regimen of gastric promotility agents are reasonable steps to deal with this common problem. A step-wise approach is outlined on page 8.

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. However, guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision. A full-text version of this guideline is also available. Both versions of this guideline will be revised, from time to time, as new evidence becomes available. Current versions of this guideline are available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

© Crown copyright, Province of Nova Scotia, 2004. May be reprinted with permission from *Cancer Care Nova Scotia* (1-866-599-2267).

Assessment of Nausea and Vomiting

Assessment Recommendations for Nausea and Vomiting	
	Assessment Recommendations
Chemotherapy treatment phase	• CTC at each treatment visit, or weekly for continuous treatment; include subjective comments on patient experience • Inpatients: assess with CTC before each chemotherapy administration or daily for continuous treatment; repeat CTC 24 hours after treatment and continue q24h for delayed or chronic N&V • If symptomatic, assess q4h until symptoms resolve
Radiotherapy treatment phase	• CTC weekly or at review clinic visit
Follow-up after active treatment phase	• CTC at scheduled follow-up visits immediately after active treatment phase, if nausea or vomiting were problematic during active treatment; follow until symptoms resolved

Symptom of cancer (usually advanced)	• CTC at each visit if symptomatic with nausea or vomiting; may assess and follow as required by severity of symptoms
	• Detailed physical history and physical examination at start and repeated at each visit
	  • If patient admitted to hospital, assess with CTC daily until symptoms resolved
	  • If patient cannot use CTC, consider using Graphic Rating Scale

Common Toxicity Criteria (CTC)	
Grade	**Nausea**
0	none
1	loss of appetite without alteration in eating habits
2	oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs
3	inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 hrs
4	Life-threatening consequences
	Vomiting
0	none
1	1 episode in 24 hours; IV fluids indicated <24 hrs
2	2-5 episodes in 24 hours
3	≥6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24 hrs
4	Life-threatening consequences

Graphic Rating Scale for Nausea

Antiemetic Agents for Management of Treatment-Induced Nausea and Vomiting

Pre-Chemotherapy Drugs & Doses- High-Risk Chemotherapy

Serotonin (5HT3) Receptor Antagonist

- Ondansetron (Zofran) 8 mg PO or IV
  OR
- Granisetron (Kytril) 2 mg PO or 1 mg IV
  OR
- Dolasetron (Anzemet) 100-200 mg PO or 100 mg IV
  PLUS

Corticosteroid

- Dexamethasone (Decadron) 8-20 mg PO or IV
  (Higher doses for highly emetogenic chemo)
  All doses given 15-30 minutes prior to chemotherapy

Intermediate-Risk Chemotherapy

Corticosteroid

- Dexamethasone 4-8 mg PO, once before chemotherapy
  AND/OR

Dopamine Receptor Antagonist

- Metoclopramide (Maxeran) 10-20 mg PO before chemotherapy
  OR
- Prochlorperazine (Stemetil) 10 mg PO before chemotherapy

Other Drugs and Doses to Consider- Neurokinin-1 (NK1) Receptor Antagonist

Aprepitant (Emend) 125 mg PO pre-chemo
Aprepitant (Emend) 80 mg PO once daily on Days 2 & 3
Notes:

- Not currently available in Canada
- If NK1 Receptor antagonist given, Serotonon RA or Dopamine RA would not be needed for delayed emesis prevention

Post-Chemotherapy Drugs & Doses- High-Risk Chemotherapy

Corticosteroid

- Dexamethasone 8 mg PO once or twice daily for 2 to 3 days (3-4 days with cisplatin)
  PLUS

Serotonin Receptor Antagonist or Dopamine Receptor Antagonist

- Ondansetron 8 mg PO q12h for 3 doses
- (Granisetron or Dolasetron effective with only pre-chemo dose, but may be given q24h for one dose)
  OR
- Metoclopramide 10-20 mg PO 2 to 4 times per day for 2 to 3 days (3-4 days with cisplatin)
- May add Diphenhydramine (Benadryl) 25-50 mg PO, to prevent extrapyramidal reactions
  OR
- Prochlorperazine 10mg PO q4-6h PRN

Intermediate-Risk Chemotherapy

- Prochlorperazine 10 mg PO q4-6h PRN
- Metoclopramide 10 mg PO q4h PRN

Adjuvant Drugs and Doses

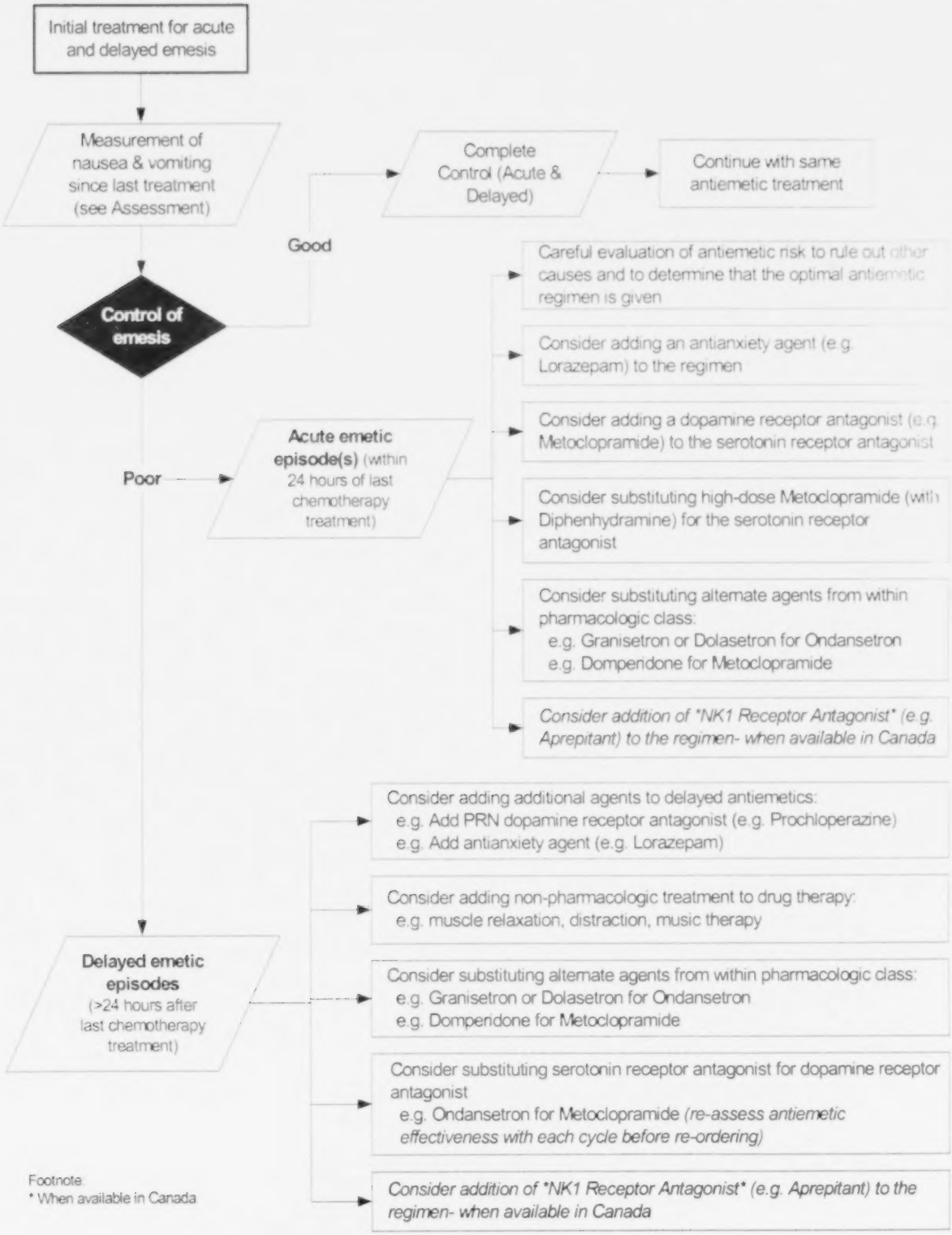
(May add to other antiemetic regimens)

- Lorazepam (Ativan) 1-2 mg PO or SL before chemotherapy
- Dronabinol (Marinol) 2.5-10 mg q4-12h OR Nabilone (Cesamet) 1-2 mg PO BID- for selected patients only

Initial Antiemetic Treatment for Adult Chemotherapy Patients

When available in Canada

Ongoing Antiemetic Treatment for Adult Chemotherapy Patients


Initial treatment for acute and delayed emesis
Measurement of nausea & vomiting since last treatment (see Assessment)
Control of emesis
Good
Complete Control (Acute & Delayed)
Continue with same antiemetic treatment
Careful evaluation of antiemetic risk to rule out other causes and to determine that the optimal antiemetic regimen is given
Consider adding an antianxiety agent (e.g. Lorazepam) to the regimen
Consider adding a dopamine receptor antagonist (e.g. Metoclopramide) to the serotonin receptor antagonist
Poor
Acute emetic episode(s) (within 24 hours of last chemotherapy treatment)
Consider substituting high-dose Metoclopramide (with Diphenhydramine) for the serotonin receptor antagonist
Consider substituting alternate agents from within pharmacologic class:
e.g. Granisetron or Dolasetron for Ondansetron
e.g. Domperidone for Metoclopramide
Consider addition of *NK1 Receptor Antagonist* (e.g. Aprepitant) to the regimen- when available in Canada
Consider adding additional agents to delayed antiemetics:
e.g. Add PRN dopamine receptor antagonist (e.g. Prochloperazine)
e.g. Add antianxiety agent (e.g. Lorazepam)
Consider adding non-pharmacologic treatment to drug therapy:
e.g. muscle relaxation, distraction, music therapy
Delayed emetic episodes (>24 hours after last chemotherapy treatment)
Consider substituting alternate agents from within pharmacologic class:
e.g. Granisetron or Dolasetron for Ondansetron
e.g. Domperidone for Metoclopramide
Consider substituting serotonin receptor antagonist for dopamine receptor antagonist
e.g. Ondansetron for Metoclopramide (re-assess antiemetic effectiveness with each cycle before re-ordering)
Consider addition of *NK1 Receptor Antagonist* (e.g. Aprepitant) to the regimen- when available in Canada

Footnote
* When available in Canada

Cancer Care Nova Scotia

Management of Nausea & Vomiting - Pediatric Cancer Patients

VERY HIGH **Rank: 4**
carmustine >250 mg/m^2
cisplatin ≥ 50 mg/m^2 *
cyclophosphamide > 1500 mg/m^2 *
dacarbazine
mechlorethamine

HIGH **Rank: 3**
carboplatin *
carmustine ≤ 250 mg/m^2
cisplatin < 50 mg/m^2 *
cyclophosphamide *
> 750 mg/m^2 and ≤ 1500 mg/m^2
cytarabine > 1000 mg/m^2
dactinomycin
daunorubicin > 60 mg/m^2
doxorubicin > 60 mg/m^2
methotrexate > 1000 mg/m^2

MODERATE **Rank: 2**
cyclophosphamide ≤ 750 mg/m^2 *
daunorubicin ≤ 60 mg/m^2
doxorubicin ≤ 60 mg/m^2
epirubicin ≤ 90 mg/m^2
etoposide ≥ 60 mg/m^2
idarubicin
ifosfamide
methotrexate = 250-1000 mg/m^2
mitoxantrone < 15 mg/m^2
Radiotherapy to abdomen, mantle, cranium, cranial spine

MILD **Rank: 1**
etoposide < 60 mg/m^2
methotrexate 51-249 mg/m^2
procarbazine
teniposide

NONE **Rank: 0**
asparaginase
bleomycin
busulfan
chlorambucil
cytarabine < 1000 mg/m^2
hydroxyurea
lomustine
mercaptopurine
methotrexate ≤ 50 mg/m^2
thioguanine
vinblastine
vincristine

Management of chemotherapy-induced nausea and vomiting in children differs from adults. Children are much more sensitive to acute dystonic reactions from dopamine receptor antagonists and are more likely to develop anticipatory nausea and vomiting. The system to rank emetogenicity of drugs and regimens includes additional gradations, to identify patients who are in greater need of higher dose antiemetics and dopamine receptor antagonists. The emetogenicity ranking of full regimens is outlined on this page, and the pediatric dosing is on the following page. Antiemetic agents for children with cancer may be given in the hospital or filled at a community pharmacy. Specific directions for antiemetic treatment will be given by the pediatric oncology program.

Regimen Emetogenicity Rank

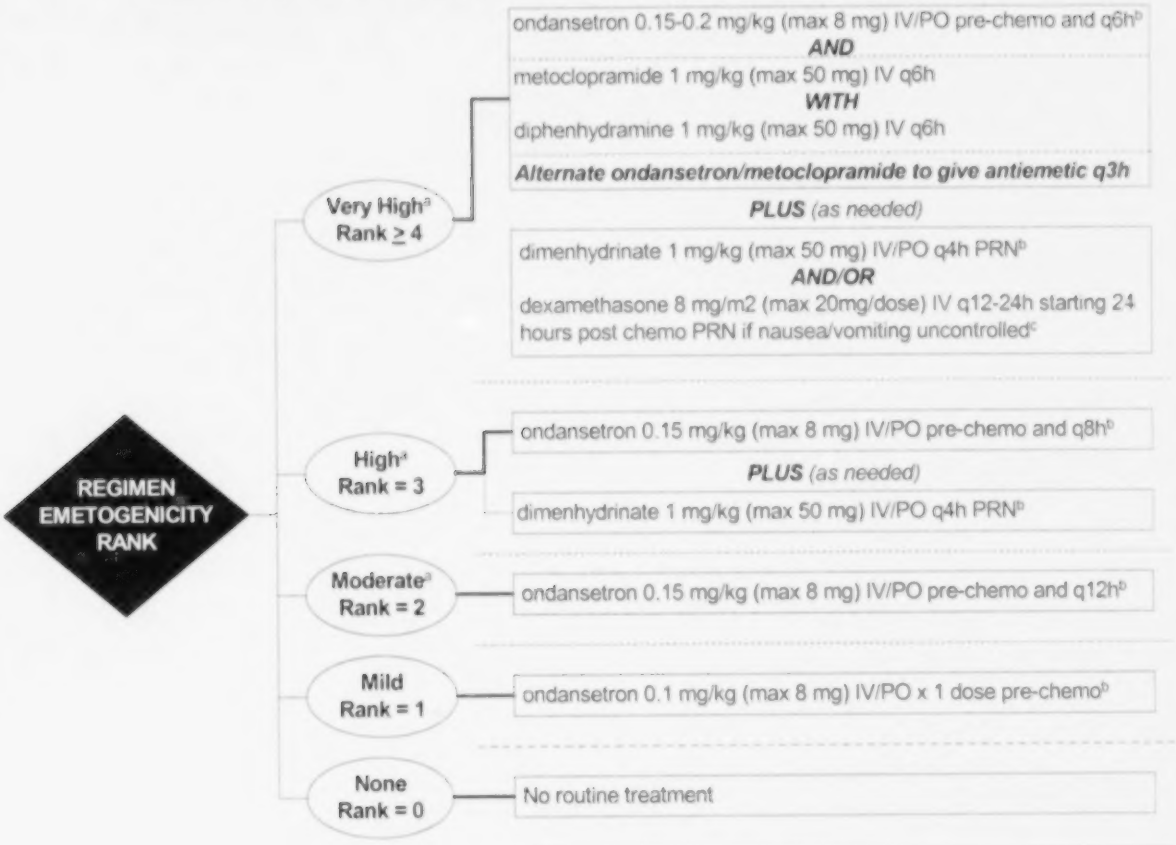
1. Start with the highest ranked individual drug
2. For every other drug to be given at the same time, and with a rank >0, add 1 rank per drug to equal the drug rank for the total regimen. (maximum rank of 5)

REGIMEN EMETOGENICITY RANK

See "**Antiemetic Treatment for Pediatric Cancer Patients**" next page

* may also cause delayed or prolonged nausea and vomiting

Antiemetic Treatment for Pediatric Cancer Patients


REGIMEN EMETOGENICITY RANK
Very High[a] Rank ≥ 4
ondansetron 0.15-0.2 mg/kg (max 8 mg) IV/PO pre-chemo and q6h[b]
AND
metoclopramide 1 mg/kg (max 50 mg) IV q6h
WITH
diphenhydramine 1 mg/kg (max 50 mg) IV q6h
Alternate ondansetron/metoclopramide to give antiemetic q3h
PLUS (as needed)
dimenhydrinate 1 mg/kg (max 50 mg) IV/PO q4h PRN[b]
AND/OR
dexamethasone 8 mg/m2 (max 20mg/dose) IV q12-24h starting 24 hours post chemo PRN if nausea/vomiting uncontrolled[c]
High[a] Rank = 3
ondansetron 0.15 mg/kg (max 8 mg) IV/PO pre-chemo and q8h[b]
PLUS (as needed)
dimenhydrinate 1 mg/kg (max 50 mg) IV/PO q4h PRN[b]
Moderate[a] Rank = 2
ondansetron 0.15 mg/kg (max 8 mg) IV/PO pre-chemo and q12h[b]
Mild Rank = 1
ondansetron 0.1 mg/kg (max 8 mg) IV/PO x 1 dose pre-chemo[b]
None Rank = 0
No routine treatment

Anticipatory Nausea/Vomiting

lorazepam (5-10 yrs: 0.5 mg/dose; > 10 yrs: 1 mg/dose) PO/SL qHS the night before chemo and/or the morning of chemo

AND

modify antiemetic regimen for next cycle of chemotherapy (i.e. increase to next rank up for regimens < rank 4)

Breakthrough Nausea/Vomiting[d]

lorazepam 0.025-0.05 mg/kg/dose (max 4 mg/dose) IV/PO/SL q6h PRN

OR

dimenhydrinate 1 mg/kg/dose IV/PO q4h PRN[b]

AND

increase ondansetron dosing frequency (e.g. from q8h to q6h)[e]

AND

add dexamethasone, if appropriate[c]

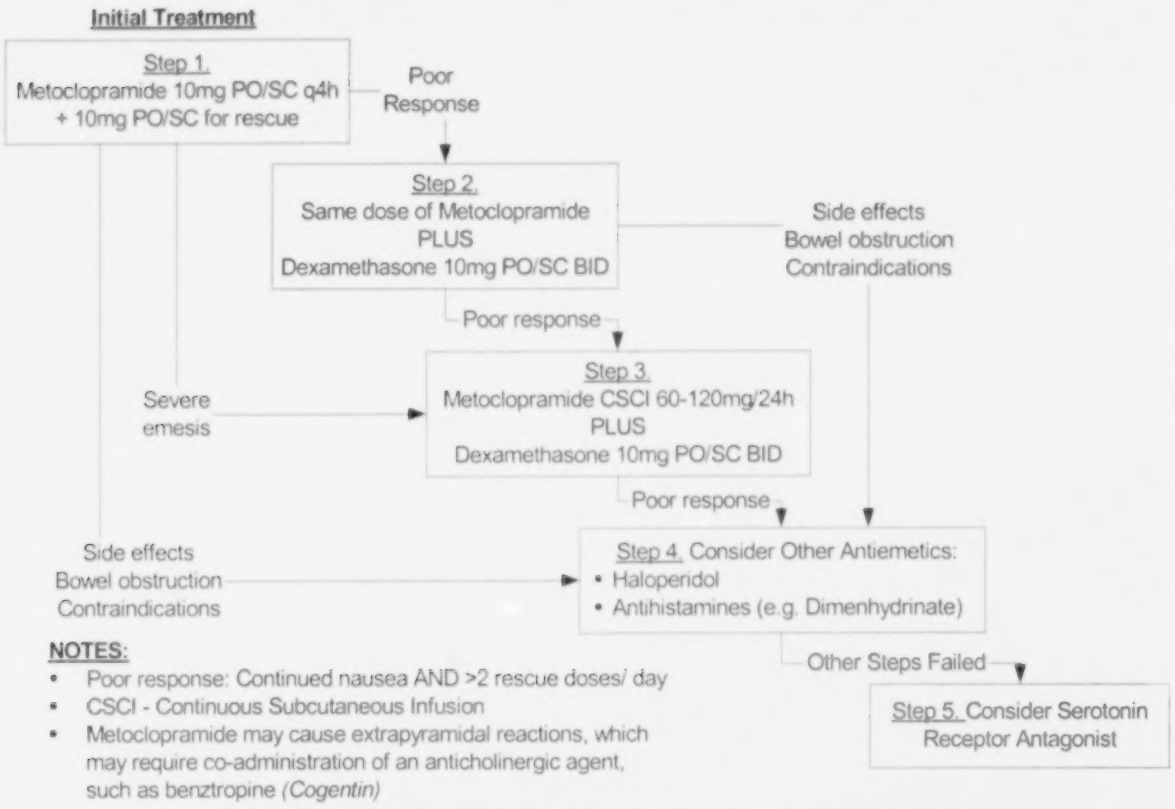
AND

modify antiemetic regimen for next cycle of chemotherapy (i.e. increase to next rank up for regimens < rank 4)

a. Regular antiemetics given 'round-the-clock' for twice the number of chemotherapy days, up to a duration of +3 days after chemotherapy. PRN antiemetics may be continued beyond this time.
b. Antiemetics given orally when appropriate. Oral Ondansetron rounded to nearest dose of 4mg or 8mg tablet or appropriate dose of liquid
c. Dexamethasone as an antiemetic may be contraindicated in some protocols or in patients receiving treatment for brain tumours.
d. Breakthrough occurs when the patient experiences > 2 vomits or retches within a 24 hour period, or experiences ≥ 3 hours of significant nausea per day, affecting the level of patient activity.
e. If patient fails on 2 consecutive cycles with ondansetron, substitute granisetron for ondansetron.

Cancer Care Nova Scotia

Antiemetic Treatment for Chronic Nausea



NOTES:

- Poor response: Continued nausea AND >2 rescue doses/ day
- CSCI - Continuous Subcutaneous Infusion
- Metoclopramide may cause extrapyramidal reactions, which may require co-administration of an anticholinergic agent, such as benztropine *(Cogentin)*

Antiemetic Treatment for Radiotherapy Patients

Radiotherapy is available only at a cancer centre. Antiemetic treatment will usually be determined by a radiation oncologist.

Assess Emetogenic Risk of Radiotherapy:
- risk by field size, location and dosage

ANTIEMETIC DRUGS AND DOSES

Serotonin Receptor Antagonists
- Ondansetron 8mg PO (may use ODT formulation) Q12H OR
- Granisetron 2mg PO OR
- Dolasetron 100-200mg PO

Dopamine Receptor Antagonists
- Prochlorperazine 10mg PO OR
- Metoclopramide 10-20mg PO

Corticosteroid
- Dexamethasone 4mg PO QD

HIGH Risk
Total Body Irradiation

Daily before first fraction and 12 hours later (i.e. twice daily):
- Serotonin receptor antagonist PLUS corticosteroid
- Dopamine receptor antagonist PRN only

INTERMEDIATE Risk
- Hemibody Irradiation
- Upper abdomen
- Abdominal-Pelvic
- Mantle
- Nasopharynx
- Cranium (radiosurgery)
- Craniospinal

Before each fraction and 12 hours later (i.e. twice daily):
- Serotonin receptor antagonist PLUS corticosteroid (and dopamine receptor antagonist PRN only); or
- Dopamine receptor antagonist +/- corticosteroid

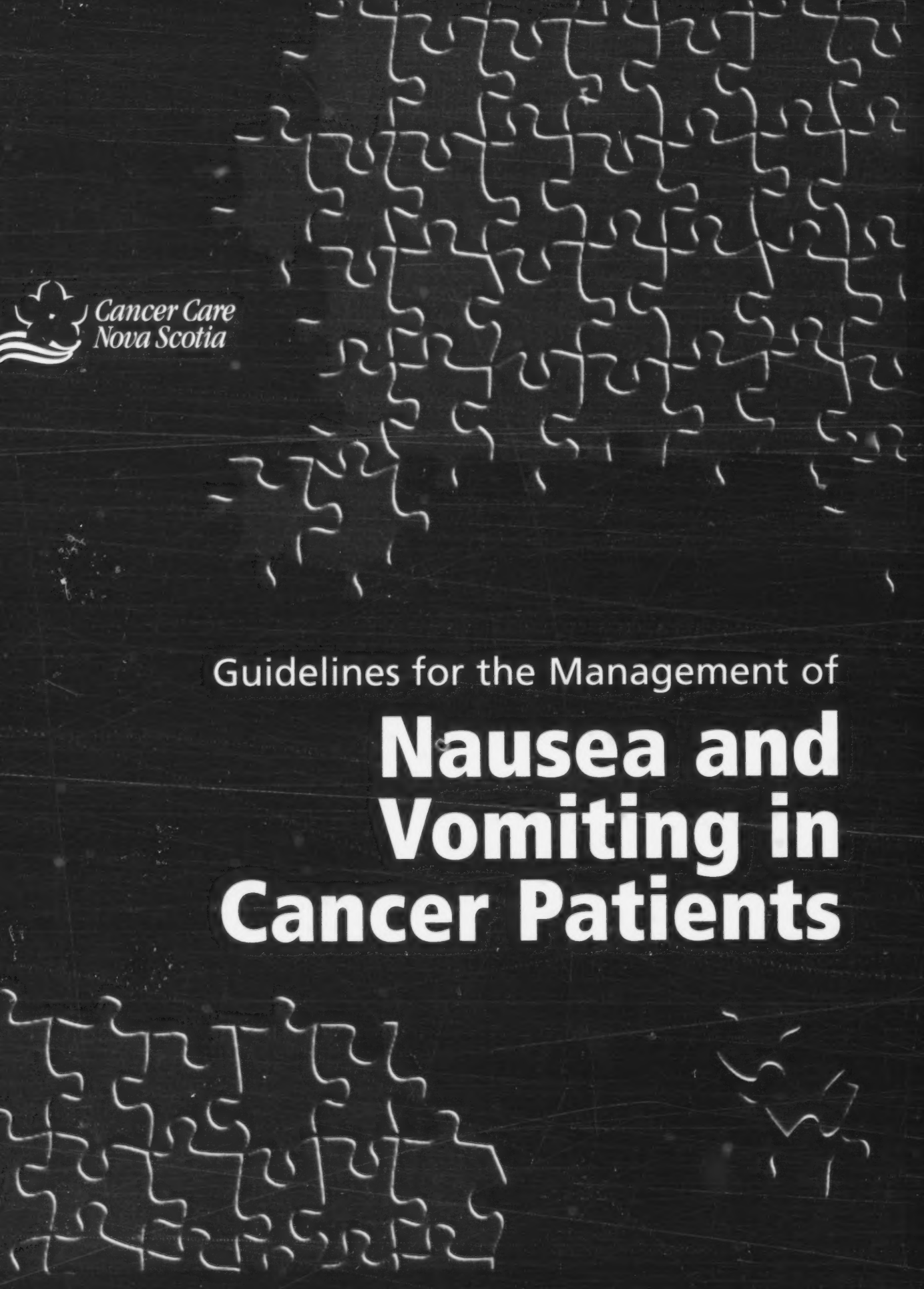
LOW Risk
- Cranium only
- Breast
- Head and neck (other than nasopharynx)
- Extremities
- Pelvis
- Thorax

As-needed basis:
- Dopamine receptor antagonist, or
- Corticosteroid, or
- Serotonin receptor antgonist

1278 Tower Road
5th floor Bethune Building
Halifax, Nova Scotia B3H 2Y9

Phone: 902-473-4645
Toll free: 1-866-599-2267
Fax: 902-473-4631

Email: info@ccns.nshealth.ca
www.cancercare.ns.ca



Guidelines for the Management of

Nausea and Vomiting in Cancer Patients

Guidelines for the Management of

Nausea and Vomiting in Cancer Patients

Guidelines for the Management of Nausea and Vomiting in Cancer Patients

Objective:

This guideline will review nausea and vomiting in cancer patients, including those receiving chemotherapy, radiotherapy, other emetogenic drug therapies, or those with chronic nausea due to disease. Evidence will be reviewed and recommendations made for assessment, treatment and other management issues. A simplified discussion with flowcharts (practice pathways) will summarize the written contents.

Preamble Note:

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. Guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision. This guideline will be revised, from time to time, as new evidence becomes available. Current versions of this guideline will be available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

These guidelines are designed for health care professionals, working in a variety of settings. For front-line health caregivers, the short version of the guidelines will be a useful reminder of assessment and treatment. This version will be useful for those who prefer to read a bit more about the recommendations. The full evidence-based discussions of these guidelines are located in the Appendices, available on request or at the *Cancer Care Nova Scotia* website. Patients, families and other non-health care professionals are recommended to review materials written for the lay public, such as the Living Well With Cancer information series. The development of these guidelines is described in Appendix XI.

Comment on Clinical Trials:

An important component of treatment decision-making for any patient is the potential for enrollment in a relevant clinical trial. The Supportive Care Cancer Site Team is committed to advancing patient care, through participation in clinical trials. At any point in time, there may be a clinical trial opportunity for any component of this guideline. As specific trials become available, eligible patients may be offered the opportunity to enroll in the relevant trial. Every effort will be made to accommodate patients for clinical trial participation, but there will be eligibility restrictions for each trial. Patients are encouraged to discuss clinical trials opportunities with their cancer specialist. Current clinical trials will be listed on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

Acknowledgements:

This guideline was written by a collaborative effort of the Supportive Care Cancer SiteTeam, and was sponsored by *Cancer Care Nova Scotia*. Portions of this practice guideline have been adapted and updated from guidelines published by the American Society of Clinical Oncology. The guidelines also incorporate knowledge of current evidence by the cancer experts in Nova Scotia.

For further information on this, or any other Practice Guideline, please contact the CST Co-Chairs, or members of the Guidelines Resource Team, *Cancer Care Nova Scotia* (contact person Michele Moore, Tel. 473-3152 or by email michele.moore@ccns.nshealth.ca).

Contents:

Part	Title	Page
Part 1.	Introduction	3
Part 2.	Assessment of Nausea and Vomiting	13
Part 3.	Management of Nausea and Vomiting as Symptoms of Advanced Cancer	15
Part 4.	Management of Chemotherapy and Radiotherapy Treatment-Induced Nausea and Vomiting	19
	4.1 Management of Acute Chemotherapy-Induced Emesis	19
	4.2 Management of Delayed Chemotherapy-Induced Emesis	19
	4.3 Management of Anticipatory Chemotherapy-Induced Emesis	22
	4.4 Management of Nausea and Emesis in Pediatric Oncology	22
	4.5 Management of Emesis with High-Dose Chemotherapy	22
	4.6 Management of Chemotherapy-Induced Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles	22
	4.7 Management of Radiotherapy-Induced Nausea and Vomiting	25
	4.8 Management of Nausea and Vomiting Induced by Other Drugs Used in Cancer Treatment	26
	4.9 Non-Pharmacological Management of Nausea and Vomiting	27
Part 5.	Practice Pathways	28
	Appendices	A1
Appendix I	Pathophysiology & Neurophysiology of Nausea and Vomiting	A2
Appendix II	Evidence-Based Recommendations: Assessment of Nausea and Vomiting	A5
Appendix III	Evidence-Based Recommendations: Pharmacologic Agents for the Treatment of Nausea and Vomiting	A12
Appendix IV	Evidence-Based Recommendations: Treatment of Chemotherapy-Induced Nausea and Vomiting	A47
Appendix V	Evidence-Based Recommendations: Treatment of Radiotherapy-Induced Nausea and Vomiting	A68
Appendix VI	Evidence-Based Recommendations: Treatment of Nausea and Vomiting Induced by Other Drugs Used in Cancer Treatment	A72
Appendix VII	Evidence-Based Recommendations: Non-Pharmacological Management of Nausea and Vomiting	A75
Appendix VIII	Evidence-Based Recommendations: Management of Constipation to Reduce Nausea and Vomiting	A82
Appendix IX	Guideline Development Process	A85

Guideline Approvals:

- Supportive Care Cancer Site Team-
  - Initial date approved- 4 Mar 2003
  - Revision with Community Reviewer Input- 13 January 2004
- *Cancer Care Nova Scotia*, Commissioner- 19 January 2004

© Crown copyright, Province of Nova Scotia, 2004.
May be reprinted with permission from *Cancer Care Nova Scotia*
(1-866-599-2267).

Part 1. Introduction

Note: See Appendix I for detailed discussion on pathophysiology and neurophysiology.

1.1 Nausea and Vomiting as Symptoms of Cancer:

Chronic nausea and vomiting are common symptoms in patients with advanced cancer, occurring in approximately 21% to 68% of these patients.[1,2] The incidence of chronic nausea is greatest in the last few weeks of life. Although there is no standard definition for chronic nausea, it is often considered as nausea lasting for four weeks or longer, but this may be shorter in palliative care patients.

The underlying pathophysiology is complex, with multiple mechanisms for emesis and large variance between individual patients.[3] Treatment differs somewhat from nausea related to radiation therapy or chemotherapy. Chronic nausea can significantly impair a patient's quality of life.

1.1.1 Presenting Symptoms

The patient with chronic nausea typically presents with a variety of symptoms associated with advanced cancer. The patient may or may not have emesis with the nausea, but it is usually the nausea which impairs the patient's quality of life. A careful medical history is needed to identify any contributing factors to the chronic nausea, but often the patient is well-known to the medical care system from earlier cancer management efforts. Important factors which may contribute to chronic nausea include:

- Constipation, possibly with bowel obstruction
- Use of opioids for concurrent pain management
- Delayed chemotherapy-induced nausea and vomiting (for recently-treated patients)
- Radiation therapy
- Peptic ulcer disease
- Metabolic abnormalities, such as renal failure, hepatic failure, or hypercalcemia, which may be manifestations of the advanced cancer or may have been caused by systemic therapy of the cancer
- Increased intracranial pressure from brain metastases
- Anxiety
- Autonomic dysfunction
- Other drugs, such as anti-inflammatories or antibiotics

It is particularly important to rule out other causes than those most commonly associated with nausea and vomiting when conducting the medical history. For example, peptic ulcer or gastric distress from anti-inflammatory drugs may be overlooked when the patient is receiving chemotherapy, since the chemotherapy is assumed to be the causal factor.

References:

1. Pereira J, Bruera E: Chronic nausea. In: Bruera E, Higginson I, eds.: Cachexia-Anorexia in Cancer Patients. New York, NY: Oxford University Press, 1996, pp 23-37.
2. Baines MJ: Nausea, vomiting, and intestinal obstruction. In: Fallon M, O'Neill B, eds.: ABC of Palliative Care. London: BMJ Books, 1998, pp 16-18.
3. Bruera E, Sweeney C, Chronic nausea and vomiting. In: Berger AM, Portenoy RK, Weissman DE, Eds. Principles and Practice of Palliative Care and Supportive Oncology. Lippincott Williams & Wilkins, Philadelphia, 2002.

1.2. Nausea and Vomiting Induced by Cancer Treatment

1.2.1 Overview

Prevention and control of nausea and vomiting are significant outcomes in the supportive care of cancer patients. Adverse effects from poorly controlled nausea and vomiting may include biomedical complications, such as serious metabolic derangements, nutritional depletion and anorexia, deterioration of patients' physical and mental status, esophageal tears, fractures, or wound dehiscence. Subjective outcomes for patients may be their withdrawal from potentially useful and curative antineoplastic treatment, and degeneration of self-care and functional ability. Despite advances in pharmacologic and nonpharmacologic management, nausea and vomiting remain two of the most distressing side effects to cancer patients and their families.[1-3]

Introduction

Nausea is a subjective phenomenon of an unpleasant, wavelike sensation experienced in the back of the throat and/or the epigastrium. Nausea may or may not result in vomiting (or emesis). Vomiting is the forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral cavity. Retching is gastric and esophageal movements of vomiting without expulsion of vomitus. Retching is also referred to as "dry heaves."

Classifications

A number of classifications of nausea and vomiting (N&V) have been used in the literature[1,4] including acute, delayed, late or persistent, chronic, anticipatory, breakthrough, or refractory. N&V have also been classified in relation to the type of treatment which induced N&V (e.g., chemotherapy or radiation), and clinical course of the cancer (e.g., advanced or terminal disease).[5,6] The most commonly described types are acute, delayed, and anticipatory chemotherapy-induced N&V; and chronic N&V in advanced cancer patients. Although there are no standard definitions, the following are typically used to classify the different types.

Anticipatory nausea and vomiting (ANV): ANV is nausea and/or vomiting that occur prior to the beginning of a new cycle of chemotherapy, in response to conditioned stimuli such as the smells, sights, and sounds of the treatment room or hospital. ANV is a classically-conditioned response, which typically begins after three or four prior events of chemotherapy-induced N&V (acute or delayed) and which then continues to occur prior to all subsequent chemotherapy treatments.

Acute nausea and vomiting (or emesis): N&V experienced during the first 24-hour period after chemotherapy administration is considered acute N&V.[1] Acute N&V is often characterized by single or multiple emetic episodes, with brief experiences of nausea prior to the vomiting.

Delayed (or late) nausea and vomiting (or emesis): N&V that occurs more than 24 hours after chemotherapy administration is considered delayed, or late N&V. Delayed N&V is associated with cisplatin, cyclophosphamide, and other drugs (e.g., doxorubicin and ifosfamide) given at high doses or on two or more consecutive days. Delayed N&V may be characterized by more persistent nausea and less intense vomiting.

Chronic nausea and vomiting (or emesis) in advanced cancer patients: Chronic nausea and vomiting in the advanced cancer patient is N&V associated with a variety of potential etiologies. The causes of chronic N&V in cancer patients are not well understood, and there is relatively little research in this area. Potential causal factors may include gastrointestinal, cranial, metabolic, drug-induced (e.g., morphine), cytotoxic chemotherapy, and radiation-induced mechanisms.[7]

Note: *"Vomiting" and "Emesis" are used interchangeably throughout this document, reflecting the common interchange in the literature on this subject.*

References:

1. Wickham R: Nausea and vomiting. In: Yarbo CH, Frogge MH, Goodman M, eds.: Cancer Symptom Management. 2nd ed., Sudbury, Mass: Jones and Bartlett Publishers, 1999, pp 228-263.
2. Coates A, Abraham S, Kaye SB, et al.: On the receiving end - patient perception of the side-effects of cancer chemotherapy. European Journal of Cancer and Clinical Oncology 19(2): 203-208, 1983.
3. Craig JB, Powell BL: The management of nausea and vomiting in clinical oncology. American Journal of the Medical Sciences 293(1): 34-44, 1987.
4. Pisters KM, Kris MG: Treatment-related nausea and vomiting. In: Berger A, Portenoy RK, Weissman DE, eds.: Principles and Practice of Supportive Oncology. Philadelphia, Pa: Lippincott-Raven Publishers, 1998, pp 165-199.
5. Fallon BG: Nausea and vomiting unrelated to cancer treatment. In: Berger A, Portenoy RK, Weissman DE, eds.: Principles and Practice of Supportive Oncology. Philadelphia, Pa: Lippincott-Raven Publishers, 1998, pp 179-189.
6. Allan SG: Nausea and vomiting. In: Doyle D, Hanks GW, MacDonald N, eds.: Oxford Textbook of Palliative Medicine. 2nd ed. New York, NY: Oxford University Press, 1998, pp 282-290.
7. D'Acquisto R, Tyson LB, Gralla RJ, et al.: The influence of a chronic high alcohol intake on chemotherapy-induced nausea and vomiting. Proceedings of the American Society of Clinical Oncology 5: A-1006, 257, 1986.

1.2.3 General Risk Factors and Etiologies

Not all cancer patients will experience nausea and/or vomiting. The most common causes are emetogenic chemotherapy drugs (i.e. drugs which induce nausea and emesis) and radiation therapy to the gastrointestinal tract, liver, or brain. Several patient characteristics associated with higher risk of nausea and emesis have also been identified. These characteristics are described in Table 1.2.3. Patients with poor control of N&V during prior chemotherapy cycles are likely to experience N&V in subsequent cycles. N&V is less likely in patients with a history of chronic, high alcohol intake,[1,2] and more likely in women[3,4] and younger patients (<50 years).[3]

Table 1.2.3: Variables Found to Correlate with a Higher Incidence of Nausea and Vomiting - Patient Characteristics

Incidence and severity of nausea and vomiting (N&V) during past courses of chemotherapy *(less likely in patients who have not had a previous episode of nausea and vomiting)*
History of chronic alcohol use *(less likely in patients with positive history)*
Age *(less likely in patients ≥50 years)*
Gender *(less likely in males)*

Other possible causes of N&V in cancer patients include:

1. Fluid and electrolyte imbalances such as hypercalcemia, volume depletion, or water intoxication (over-hydration);
2. Tumor invasion or growth in the gastrointestinal tract, liver, or central nervous system, especially the posterior fossa;
3. Constipation;
4. Certain drugs such as opioids;
5. Infection or septicemia; or
6. Uremia.

The psychological variables of state anxiety, (level of anxiety during chemotherapy infusions), and pretreatment expectations for nausea and vomiting (self-fulfilling prophecy) have also been investigated as predictors of posttreatment nausea.[5-9] To date, most trials have found mixed results that vary due to different research methods. Better designed, more recent studies have found state anxiety and patient expectations for nausea to be predictors of posttreatment nausea, even after controlling for known physiological predictors (susceptibility to nausea during pregnancy and motion sickness) and emetogenetic potential of the chemotherapy drugs.[7-9] In addition, those patients with greater inherent autonomic nervous system reactivity were notably more likely to experience nausea 24 hours or more after chemotherapy[10], suggesting another future opportunity to identify patients at high risk of post-chemotherapy nausea.

Clinicians treating N&V must be alert to all potential causes and factors, especially in cancer patients who may be receiving combinations of several treatments and medications and who may have underlying risk factors.

References:

1. D'Acquisto R, Tyson LB, Gralla RJ, et al.: The influence of a chronic high alcohol intake on chemotherapy-induced nausea and vomiting. Proceedings of the American Society of Clinical Oncology 5: A-1006, 257, 1986.
2. Sullivan JR, Leyden MJ, Bell R: Decreased cisplatin-induced nausea and vomiting with chronic alcohol ingestion. New England Journal of Medicine 309(13): 796, 1983.
3. Tonato M, Roila F, Del Favero A: Methodology of antiemetic trials: a review. Annals of Oncology 2(2): 107-114, 1991.
4. Roila F, Tonato M, Basurto C, et al.: Antiemetic activity of high doses of metoclopramide combined with methylprednisolone versus metoclopramide alone in cisplatin-treated cancer patients: a randomized double-blind trial of the Italian Oncology Group for Clinical Research. Journal of Clinical Oncology 5(1): 141-149, 1987.
5. Cassileth BR, Lusk EJ, Bodenheimer BJ, et al.: Chemotherapeutic toxicity—the relationship between patients' pretreatment expectations and posttreatment results. American Journal of Clinical Oncology 8(5): 419-425, 1985.
6. Andrykowski MA, Gregg ME: The role of psychological variables in post-chemotherapy nausea: anxiety and expectation. Psychosomatic Medicine 54(1): 48-58, 1992.
7. Jacobsen PB, Andrykowski MA, Redd WH, et al.: Nonpharmacologic factors in the development of posttreatment nausea with adjuvant chemotherapy for breast cancer. Cancer 61(2): 379-385, 1988.
8. Haut MW, Beckwith BE, Laurie JA, et al.: Postchemotherapy nausea and vomiting in cancer patients receiving outpatient chemotherapy. Journal of Psychosocial Oncology 9(1): 117-130, 1991.
9. Roscoe JA, Hickok JT, Morrow GR: Patient expectations as predictor of chemotherapy-induced nausea. Annals of Behavioral Medicine 22(2): 121-126, 2000.
10. Morrow GR, Hickok JT, DuBeshter B, Lipschultz SE: Changes in clinical measures of autonomic nervous system function related to cancer chemotherapy-induced nausea. J Auton Nerv Syst 78(1): 57-63, 1999.

1.2.4 Anticipatory Nausea and Vomiting

Prevalence

Variable prevalence of anticipatory nausea and vomiting (ANV) has been reported in the literature, due to different definitions and assessment methods.[1] Anticipatory nausea (AN) appears to occur in about 29% of patients receiving chemotherapy, or about 1 patient in 3 or 4 , while anticipatory vomiting (AV) appears to occur in 11% of patients, or about 1 patient in 9.[2] When serotonin receptor antagonists were introduced, it was expected that ANV would decline, however not all recent studies have had the expected results. One study found a lower incidence of ANV,[3] and three studies found comparable incidence rates.[2,4,5] It appears that the serotonin receptor antagonist agents reduce postchemotherapy vomiting, but not postchemotherapy nausea,[2,5] and the resulting impact on ANV is unclear.

Classical Conditioning

A number of theoretical mechanisms have been proposed to explain ANV[6]. ANV is best explained by classical conditioning (also known as Pavlovian or respondent conditioning).[7] In classical conditioning, a previously neutral stimulus (e.g., smells of the chemotherapy environment) comes to elicit a conditioned response (e.g., ANV) after a number of prior pairings, or 'learning trials'. In cancer chemotherapy the first few chemotherapy infusions are the 'learning trials'. The chemotherapy drugs are the unconditioned stimuli that elicit postchemotherapy nausea and vomiting (in some patients). They are paired with a variety of other neutral, environmental stimuli (e.g., smells of the setting, oncology nurse, chemotherapy room). These previously neutral stimuli then become conditioned stimuli and elicit ANV in future chemotherapy cycles. ANV is not an indication of psychopathology, but rather a learned response that, in other life situations (e.g., food poisoning) results in adaptive avoidance. A variety of correlational studies provide empirical support for classical conditioning. For example, the prevalence of ANV prior to any chemotherapy is very rare, and few patients ever experience ANV without prior postchemotherapy nausea.[8] Also, most studies have found a higher probability of ANV with increasing numbers of chemotherapy infusions, and the intensity of ANV increases as patients get closer to the actual time of their infusion.[9] In one experimental study, it was shown that a novel beverage could become a conditioned stimulus to nausea when paired with several chemotherapy treatments.[10]

Variables Correlated with ANV

Many variables have been investigated as potential factors that correlate with the incidence of ANV in hopes of developing a list of "risk factors." There is currently no agreement on which factors predict ANV. A patient with fewer than three of the following eight characteristics is unlikely to develop ANV, and that screening following the first chemotherapy infusion could identify those patients at increased risk.[11]

Table 1.2.4: Variables Found to Correlate with ANV - Patient Characteristics
Age less than 50
Nausea/vomiting after last chemotherapy session
Posttreatment nausea described as "moderate, severe, or intolerable"
Posttreatment vomiting described as "moderate, severe, or intolerable"
Feeling warm or hot all over after last chemotherapy session
Susceptibility to motion sickness
Sweating after last chemotherapy session
Generalized weakness after last chemotherapy session

From:
Morrow GR, Roscoe JA, Hickok JT: Nausea and vomiting. In: Holland JC, Breitbart W, Jacobsen PB, et al., eds.: Psycho-oncology. New York, NY: Oxford University Press, 1998, pp 476-484.

Other variables that have been found to correlate with ANV include the following: high state anxiety (anxiety reactive to specific situations);[12] greater reactivity of the autonomic nervous system, and slower reaction time;[13] patient expectations of chemotherapy related nausea before beginning treatment;[14] percentage of infusions of chemotherapy followed by nausea;[15] postchemotherapy dizziness, lightheadedness, and longer latency of onset of posttreatment nausea and vomiting.[16] Finally, a very important correlate is the emetogenic potential of various chemotherapeutic agents. Not surprisingly, those patients receiving drugs with a moderate to severe potential for posttreatment nausea and vomiting are more likely to develop ANV.[12]

References:

1. Andrykowski MA: Defining anticipatory nausea and vomiting: differences among cancer chemotherapy patients who report pretreatment nausea. Journal of Behavioral Medicine 11(1): 59-69, 1988.
2. Morrow GR, Roscoe JA, Kirshner JJ, et al.: Anticipatory nausea and vomiting in the era of 5-HT3 antiemetics. Supportive Care in Cancer 6(3): 244-247, 1998.
3. Aapro MS, Kirchner V, Terrey JP: The incidence of anticipatory nausea and vomiting after repeat cycle chemotherapy: the effect of granisetron. British Journal of Cancer 69(5): 957-960, 1994.
4. Fernandez-Marcos A, Martin M, Sanchez JJ, et al.: Acute and anticipatory emesis in breast cancer patients. Supportive Care in Cancer 4(5): 370-377, 1996.
5. Roscoe JA, Morrow GR, Hickok JT, et al.: Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. Journal of Pain and Symptom Management 20(2): 113-121, 2000.
6. Reesal RT, Bajramovic H, Mai F: Anticipatory nausea and vomiting: a form of chemotherapy phobia? Canadian Journal of Psychiatry 35(1): 80-82, 1990.
7. Stockhorst U, Klosterhalfen S, Steingruber HJ: Conditioned nausea and further side-effects in cancer chemotherapy: a review. Journal of Psychophysiology 12(suppl 1): 14-33, 1998.
8. Morrow GR, Rosenthal SN: Models, mechanisms and management of anticipatory nausea and emesis. Oncology 53(suppl 1): 4-7, 1996.
9. Montgomery GH, Bovbjerg DH: The development of anticipatory nausea in patients receiving adjuvant chemotherapy for breast cancer. Physiology and Behavior 61(5): 737-741, 1997.
10. Bovbjerg DH, Redd WH, Jacobsen PB, et al.: An experimental analysis of classically conditioned nausea during cancer chemotherapy. Psychosomatic Medicine 54(6): 623-637, 1992.
11. Morrow GR, Roscoe JA, Hickok JT: Nausea and vomiting. In: Holland JC, Breitbart W, Jacobsen PB, et al., eds.: Psycho-oncology. New York, NY: Oxford University Press, 1998, pp 476-484.

12. Andrykowski MA, Redd WH, Hatfield AK: Development of anticipatory nausea: a prospective analysis. Journal of Consulting and Clinical Psychology 53(4): 447-454, 1985.
13. Kvale G, Psychol C, Hugdahl K: Cardiovascular conditioning and anticipatory nausea and vomiting in cancer patients. Behavioral Medicine 20(2): 78-83, 1994.
14. Montgomery GH, Tomoyasu N, Bovbjerg DH, et al.: Patients' pretreatment expectations of chemotherapy-related nausea are an independent predictor of anticipatory nausea. Annals of Behavioral Medicine 20(2): 104-109, 1998.
15. Tomoyasu N, Bovbjerg DH, Jacobsen PB: Conditioned reactions to cancer chemotherapy: percent reinforcement predicts anticipatory nausea. Physiology and Behavior 59(2): 273-276, 1996.
16. Chin SB, Kucuk O, Peterson R, et al.: Variables contributing to anticipatory nausea and vomiting in cancer chemotherapy. American Journal of Clinical Oncology 15(3): 262-267, 1992.
17. Carey MP, Burish TG: Etiology and treatment of the psychological side effects associated with cancer chemotherapy: a critical review and discussion. Psychological Bulletin 104(3): 307-325, 1988.
18. Lyles JN, Burish TG, Krozely MG, et al.: Efficacy of relaxation training and guided imagery in reducing the aversiveness of cancer chemotherapy. Journal of Consulting and Clinical Psychology 50(4): 509-524, 1982.
19. Redd WH, Andreson GV, Minagawa RY: Hypnotic control of anticipatory emesis in patients receiving cancer chemotherapy. Journal of Consulting and Clinical Psychology 50(1): 14-19, 1982.
20. Morrow GR, Morrell C: Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. New England Journal of Medicine 307(24): 1476-1480, 1982.
21. Burish TG, Shartner CD, Lyles JN: Effectiveness of multiple muscle-site EMG biofeedback and relaxation training in reducing the aversiveness of cancer chemotherapy. Biofeedback and Self Regulation 6(4): 523-535, 1981.
22. Kolko DJ, Rickard-Figueroa JL: Effects of video games on the adverse corollaries of chemotherapy in pediatric oncology patients: a single-case analysis. Journal of Consulting and Clinical Psychology 53(2): 223-228, 1985.
23. Vasterling J, Jenkins RA, Tope DM, et al.: Cognitive distraction and relaxation training for the control of side effects due to cancer chemotherapy. Journal of Behavioral Medicine 16(1): 65-80, 1993.

1.2.5 Acute/Delayed Emesis

Acute Emesis

Etiologies

Chemotherapy is the most common treatment-related cause of nausea and vomiting. The incidence and severity of acute emesis in persons receiving chemotherapy varies according to many factors, including the particular drug, dose, schedule of administration, route, and individual patient variables (e.g. anxiety, level of distress). In the majority of cancer patients, these symptoms can be prevented or controlled.

Risk Factors

Risk factors for acute emesis include poor control with prior chemotherapy, female gender, and younger age.[1]

Emetic Classifications

The American Society of Clinical Oncology (ASCO) has developed a rating system for chemotherapeutic agents and their respective risk of acute and delayed emesis.[1] These drugs are stratified within each category by their approximate emetogenic potential (i.e. drugs higher in the list are likely more emetogenic). Clinical experience suggests some small modification to this classification, for drugs that are used in different dosage forms (e.g., cyclophosphamide, melphalan in both IV and oral formulations).

Table 1.2.5: Emetic Risk from Various Chemotherapeutic Agents	
Acute Emetic Category	**Chemotherapy Agent (trade name)**
High: cisplatin • Emesis that has been documented to occur in more than 99% of patients	cisplatin (Platinol)
High: noncisplatin • Emesis that has been documented to occur in 30% to greater than 90% of patients	dacarbazine (DTIC) dactinomycin (Cosmegen) carmustine (BiCNU) mechlorethamine (Mustargen) melphalan IV (Alkeran) busulfan (high dose) streptozotocin (Zanosar) hexamethylmelamine (Hexalen) carboplatin (Paraplatin) cyclophosphamide IV (Cytoxan) lomustine (CeeNU) daunorubicin (Cerubidine) doxorubicin (Adriamycin) epirubicin (Pharmorubicin) idarubicin (Idamycin) cytarabine (Cytosar) ifosfamide (Ifex) irinotecan (Camptosar)
Intermediate • Emesis that has been documented to occur in 10% to 30% of patients	mitoxantrone (Novantrone) paclitaxel (Taxol) docetaxel (Taxotere) mitomycin (Mutamycin) topotecan (Hycamptin) gemcitabine (Gemzar) cyclophosphamide PO (Cytoxan) etoposide (Vepesid) teniposide (Vumon)
Low • Emesis that has been documented to occur in less than 10% of patients	vinorelbine (Navelbine) fluorouracil methotrexate thioguanine (Lanvis) mercaptopurine (Purinethol) bleomycin (Blenoxane) asparaginase (Kidrolase) vindesine (Eldisine) vinblastine (Velban) vincristine (Oncovin) busulphan (Myleran) chlorambucil (Leukeran) melphalan PO (Alkeran) hydroxyurea (Hydrea) fludarabine (Fludara) cladribine (Leustatin)

Adapted from: Gralla RJ, Osoba D, et al, for the American Society of Clinical Oncology: Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. Journal of Clinical Oncology 17(9): 2971-2994, 1999.

In addition to emetogenic potential, the dose and schedule used are also extremely important factors. For example, a drug with a low emetogenic potential given in high doses may cause a dramatic increase in the potential to induce nausea and vomiting. Standard doses of cytarabine rarely produce nausea and vomiting, but these are often seen with high doses of this drug (see (4.5 High Dose Chemotherapy and Appendix IV.e) and individual regimen descriptions for further details). Likewise, drugs with high emetogenic potential may be given at much lower doses with significantly reduced nausea and vomiting (e.g. small daily doses of cisplatin given concurrent with radiotherapy evoke very little nausea and vomiting). Another factor to consider is the use of drug combinations. Because most patients receive combination chemotherapy, the emetogenic potential of all of the drugs combined and individual drug doses needs to be considered.

Delayed Emesis

Delayed (or late) nausea and vomiting (emesis): nausea and vomiting that occurs 24 hours or more after chemotherapy administration is considered delayed, or late nausea and vomiting. Delayed nausea and vomiting is associated with cisplatin, cyclophosphamide, and other drugs (e.g., doxorubicin and ifosfamide) given at high doses or on two or more consecutive days.

Etiologies

Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis. It is suggested that poorly controlled delayed nausea and vomiting may be largely responsible for the continued incidence of anticipatory N&V as well.

Risk Factors

All predicative characteristics for acute emesis should be considered a risk factor for delayed. Delayed emesis has been associated with high levels of morbidity and there are fewer treatment options with proven efficacy.[2-4]

References:

1. Gralla RJ, Osoba D, et al, for the American Society of Clinical Oncology: Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. Journal of Clinical Oncology 17(9): 2971-2994, 1999.
2. Navari RM, Reinhardt RR, et al, for the L-754,030 Antiemetic Trial Group: Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. New England Journal of Medicine 340(3): 190-195, 1999.
3. Hesketh PJ, Gralla RJ, Webb RT, et al.: Randomized phase II study of the neurokinin 1 receptor antagonist CJ-11,974 in the control of cisplatin-induced emesis. Journal of Clinical Oncology 17(1): 338-343, 1999.
4. The Italian Group for Antiemetic Research: Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. New England Journal of Medicine 342(21): 1554-1559, 2000.

1.2.6 Radiation Therapy

Correlates

Patients receiving radiation to the GI tract or brain have the greatest potential for nausea/vomiting as a side effect. Because cells of the GI tract excrete serotonin and are populated with serotonin receptors, they may be quite sensitive to increased serotonin release secondary to radiation therapy. Radiation to the brain is believed to stimulate the brain's vomiting center or CTZ (chemotherapy trigger zone). Similar to chemotherapy, radiation dose/ fractionation factors also play a role in determining the possible occurrence of nausea and vomiting. In general, the higher the daily fractional dose and the

greater the amount of tissue that is irradiated, the higher the potential for nausea and vomiting. In addition, the larger the amount of GI tract irradiated (particularly for fields that include the small intestine and stomach), the higher the potential for nausea and vomiting. Total-body irradiation before bone marrow transplant, for example, has a high probability of inducing nausea and vomiting as acute side effects.

Prevalence

Nausea and vomiting from radiation may be acute and self-limiting, usually occurring one-half to several hours after treatment. Patients report that symptoms improve on days that they are not being treated. There are also cumulative effects that may occur in patients receiving radiation therapy to the GI tract. [1]

References:

1. Gralla RJ, Osoba D, et al, for the American Society of Clinical Oncology: Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. Journal of Clinical Oncology 17(9): 2971-2994, 1999.

Part 2. Assessment of Nausea and Vomiting

Note: See Appendix II for detailed discussion and evidence-based recommendations.

When nausea and vomiting present as a symptom of cancer, an initial medical assessment to determine the cause is the first step in assessment. Patients who continue to experience nausea and/or vomiting, as symptoms of their cancer should be assessed on a regular basis. Assessment may be documented using the Common Toxicity Criteria scale (see Table 2.1), or a suitable alternative (e.g. Visual Analog Scale, Graphic Rating Scale), as appropriate to the patient. Subjective patient experiences and health care provider observations are equally important in the assessment. The assessments should be easily correlated to interventions, to determine success. Numeric assessment scores should be accompanied by other subjective observations, appropriate to the individual patient situation.

Patients on active chemotherapy, or radiotherapy to the brain or gastrointestinal (GI) tract, should be assessed on a regular basis with the Common Toxicity Criteria scale, to screen for evidence of nausea and/or vomiting. Subjective patient reports of nausea must be accepted at face value. Emetic episodes must be documented for inpatients or determined from patient self-reports for outpatients.

Recommended assessment frequencies are outlined in Table 2.2.

Table 2.1 - Common Toxicity Criteria (CTC)

Adverse Event Grade	Nausea
0	None
1	Loss of appetite without alteration in eating habits
2	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs
3	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 hrs
4	Life-threatening consequences
	Vomiting
0	None
1	1 episode in 24 hours; IV fluids indicated <24 hrs
2	2-5 episodes in 24 hours
3	≥6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24 hrs
4	Life-threatening consequences
	Dehydration
0	None
1	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor
2	IV fluids indicated for <24 hrs
3	IV fluids indicated for ≥ 24 hrs
4	Life-threatening consequences (e.g., hemodynamic collapse)

Figure 1. Graphic Rating Scale for Nausea

Recommendations for Nausea and Vomiting	
	Assessment Recommendations
Chemotherapy treatment phase	• CTC at each treatment visit, or weekly for continuous treatment; include subjective comments on patient experience • Inpatients: assess with CTC before each chemotherapy administration or daily for continuous treatment; repeat CTC 24 hours after treatment and continue q24h for delayed or chronic N&V • If symptomatic, assess q4h until symptoms resolve
Radiotherapy treatment phase	• CTC weekly or at review clinic visit
Follow-up after active treatment phase	• CTC at scheduled follow-up visits immediately after active treatment phase, if nausea or vomiting were problematic during active treatment; follow until symptoms resolved
Symptom of cancer (usually advanced)	• CTC at each visit if symptomatic with nausea or vomiting; may assess and follow as required by severity of symptoms • Detailed physical history and physical examination at start and repeated at each visit • If patient admitted to hospital, assess with CTC daily until symptoms resolved • If patient cannot use CTC, consider using Graphic Rating Scale

Part 3. Management of Nausea and Vomiting as Symptoms of Advanced Cancer

3.1 Management of Nausea and Vomiting

3.1.1 General Supportive Care

Management of chronic nausea centers on identifying the underlying causes, addressing these where possible, and controlling the symptoms.[1,2] A basic working knowledge of the emetic and nauseagenic pathways and identification of possible underlying causes should guide management strategy and antiemetic selection.

General support measures should be in place throughout the care of patients with chronic nausea. Good oral hygiene may help reduce nausea. A comfortable environment, regular baths to reduce unpleasant body odors, and attention to diet and hydration should be considerations in the routine support of patients with advanced cancer.

3.1.2 Management of Underlying Causes

When an underlying cause is identified, this cause should be addressed to reduce or eliminate chronic nausea. Metabolic imbalances should be corrected whenever possible. If opioid toxicity is suspected, consider rotation to an alternate opioid analgesic at equianalgesic doses, to maintain pain control. This may reduce the nausea, although there may be a temporary period (up to two days) with nausea and vomiting as the patient acclimatizes to the new analgesic. A comprehensive medication review should be included in the assessment process, and any unnecessary medications should be discontinued. If emetogenic medications continue to be required, consider alternate medication choices which may be less emetogenic. If the patient has concurrent brain metastases, corticosteroids or radiotherapy for symptom control may help reduce chronic nausea. Concurrent peptic ulcer disease should be treated appropriately.

When a patient is constipated or is diagnosed with stool impaction, aggressive bowel care should be implemented. If the bowel is obstructed, surgical intervention should be considered. It is important to exclude the use of prokinetic agents if bowel obstruction is known or suspected. The management of constipation and bowel obstruction is described in Table 3.1.

3.1.3 Drug Therapy for Chronic Nausea

Multiple antiemetic regimens have been proposed for the management of chronic nausea in the setting of advanced cancer. Prospective studies comparing one regimen over another are lacking. For patients with chronic nausea in advanced cancer, metoclopramide is the drug of first choice to control the nausea. A step-wise regimen for metoclopramide use is outlined in Table 3.2. Domperidone may be substituted for patients who can swallow medications and who have difficulties with extrapyramidal reactions.[3] Other drug therapy choices for management of chronic nausea are described in Table 3.3.

Table 3.1: Management of Constipation		
General Measures	Regular laxative regimen	• Stool softener (e.g., docusate) plus bowel stimulant (e.g., sennosides) • Add lactulose if needed • Regular dose adjustments to maintain bowel habits
	Eliminate contributing medical factors	• Discontinue constipating drugs (e.g., iron supplements) • Avoid bulk agents (e.g., psyllium, cellulose), high fibre diets • Maintain physical activity, if possible • Maintain hydration, if possible
Therapeutic interventions	Oral laxatives	• Stool softener and bowel stimulant, if not already part of the regular laxative regimen • Add osmotic agent (e.g., lactulose) • Saline laxatives (e.g., sodium phosphate, magnesium citrate) used to clear constipated bowel • Use with caution in patients with renal impairment or cardiac failure
	Rectal laxatives	• Suppositories of bowel stimulants (e.g., bisacodyl) • Enemas- sodium phosphate salts, mineral oil • Limit use of enemas in advanced cancer patients, due to risk of bleeding or infection in myelosuppressed patients
	Surgical disimpaction	• To clear an obstructed bowel, followed by reinstitution of the preventative laxative regimen
	Oral Naloxone for refractory narcotic bowel syndrome	• Unproven effectiveness • Risk of opiate withdrawal syndrome
Malignant bowel obstruction	Surgical management	• Resection, with ostomy for irreversible complete obstructions • Intestinal bypass procedure • Insertion of venting gastrostomy tube
	Medical management	• Avoid use of prokinetic agents if obstruction is complete • Use alternate antiemetic agents (e.g., antihistamine, haloperidol) • Consider corticosteroid (e.g., dexamethasone 6-10mg SC TID-QID) • Parenteral hydration may be helpful • Convert all drug therapy to SC or IV route • Octreotide or hyoscine butylbromide for refractory obstruction

Table 3.2: Metoclopramide Regimen for Treatment of Chronic Nausea	
Step 1	• Metoclopramide 10mg PO/SC q4h + 10mg PO/SC for rescue • Poor response after at least two days of treatment (consistent complaint of nausea and >2 extra doses of metoclopramide per day), go to Step 2 • Occasionally patients with severe emesis, go to Step 3 • Side effects or contraindication (bowel obstruction), go to Step 4
Step 2	• Metoclopramide (same dose as Step 1) + dexamethasone 10mg PO/SC BID • Poor response after at least two days of treatment, go to Step 3 • Side effects or contraindication (bowel obstruction), go to Step 4
Step 3	• Continuous subcutaneous infusion of metoclopramide (60-120mg/day) + dexamethasone 10mg PO/SC BID (may also give benztropine) • Poor response, go to Step 4
Step 4	• Other antiemetics (e.g., haloperidol, dimenhydrinate, ondansetron)

Table 3.3: Drug Therapy for Chronic Nausea in Advanced Cancer		
Drug Class	**Examples**	**Mechanism of Action**
Prokinetic Agents	metoclopramide domperidone	• Increase motility of the upper gastrointestinal tract, up to the normal level of activity • Multiple routes for metoclopramide; domperidone only available in oral route
Dopamine antagonists	Phenothiazines (chlorpromazine, prochlorperazine) Butyrophenones (haloperidol)	• Central activity- D_2 dopamine antagonists in the chemoreceptor trigger zone (CTZ) • May cause extrapyramidal adverse effects • No peripheral antidopamine activity • Consider if complete bowel obstruction (prokinetic agents contraindicated) • Butyrophenones less sedating than phenothiazines
Antihistamines	dimenhydrinate diphenhydramine	• May reduce nausea • Consider if complete bowel obstruction (prokinetic agents contraindicated) and if extrapyramidal effects are likely (dopamine antagonists not desirable) • Sedative effects
Corticosteroids	dexamethasone	• No specific mechanism of action • Reduced intracranial pressure if brain metastases • Decreased peritumoural edema (anti-inflammatory) • Reduction of pain, anorexia, asthenia
Serotonin receptor antagonists	ondansetron granisetron dolasetron	• Antagonist of peripheral serotonin$_3$ receptors in GI tract and central receptors in CTZ • No clinical trials, only case reports • May be considered if patient failed all other treatments • May cause constipation on continuous use (less likely with episodic use)

Table 3.3: Drug Therapy for Chronic Nausea in Advanced Cancer (continued)		
Drug Class	**Examples**	**Mechanism of Action**
Progestins	megestrol	• Improvements in cachexia; may be related to autonomic failure syndrome, which is associated with chronic nausea • Adrenal suppression with long term use could be a concern
Cannabinoids	dronabinol nabilone	• Central action- proposed perceptual modification in cerebral cortex, but exact antiemetic mechanism of action unknown • Only evidence of antiemetic effects in chemotherapy-induced emesis, and in symptomatic AIDS patients • Somnolence, confusion, dysphoria, visual disturbances are common adverse effects- limit use in advanced cancer patients
Thalidomide		• Central sedative and antiemetic mechanism proposed, exact mechanism unknown • Access limited • No clinical trials, only case report • Strong teratogenic effects, sedation
Octreotide		• Reduction of secretions in gastrointestinal tract- useful for patients with inoperable bowel obstruction • Reduction of nausea may be associated with improved hydration

References:

1. Pereira J, Bruera E: Chronic nausea. In: Bruera E, Higginson I, eds.: Cachexia-Anorexia in Cancer Patients. New York, NY: Oxford University Press, 1996, pp 23-37.
2. Baines MJ: Nausea, vomiting, and intestinal obstruction. In: Fallon M, O'Neill B, eds.: ABC of Palliative Care. London: BMJ Books, 1998, pp 16-18.
3. Bruera E, Seifert L, Watanabe S, et al.: Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide-based antiemetic regimen. Journal of Pain and Symptom Management 11(3): 147-153, 1996.

Part 4. Management of Chemotherapy and Radiotherapy Treatment-Induced Nausea and Vomiting

Note: See Appendices III to VII for detailed discussion and evidence-based recommendations.

4.1 Management of Acute Chemotherapy-Induced Emesis

(Vomiting Occurring 0 to 24 Hours After Chemotherapy)

4.1.1. Risk Factors for Acute Emesis

The underlying patient characteristics and the emetogenicity of the chemotherapy agents are the two major factors which predict the risk of acute emesis (emesis occurring in the first 24 hours). These factors are detailed in Table 1.2.3 and Table 1.2.5.

4.1.2. Guidelines for Prevention and Treatment of Acute Emesis

To formulate guidelines, a classification based on emetic risk is required. See Table 1.2.5 for the rationale for such a classification by emetic risk of the chemotherapy agent.

Definition of Terms

For cisplatin, high risk is defined as emesis that has been documented to occur in more than 99% of patients. For the high-risk, non-cisplatin group, the incidence of emesis is in the range of 30% to greater than 90%. Chemotherapeutic agents in the intermediate-risk category induce emesis in 10% to 30% of patients. A less than 10% risk of emesis in patients receiving chemotherapeutic drugs was categorized as low risk.

Recommended antiemetic treatments for each risk category are outlined in Table 4.1.

4.2 Management of Delayed Chemotherapy-Induced Emesis

(Vomiting Occurring > 24 Hours After Chemotherapy)

4.2.1. Risk Factors for Delayed Emesis

Risk factors for delayed emesis include patient characteristics and the chemotherapy being administered, the same as acute chemotherapy-induced emesis. Oncologists must be aware of these risk factors, to identify patients who need preventive treatment on a routine basis and individuals who may be at greater risk.

4.2.2. Guidelines for Prevention and Treatment of Acute Emesis

Recommended antiemetic treatments for each risk category are outlined in Table 4.1.

Table 4.1. Chemotherapy-Induced Emesis: Emetic Risk Categories for Chemotherapeutic Agents and Guidelines

Acute Emetic Category	Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis
High Emetic Risk: cisplatin	cisplatin (Platinol)	Pre-treatment: Serotonin Receptor Antagonist (Ondansetron 8 mg PO or IV; OR Granisetron 2 mg PO or 1mg IV; OR Dolsetron 100-200mg PO or 100 mgIV) ***Plus*** Corticosteroid (Dexamethasone 8 mg PO or IV- may give up to 20 mg for cisplatin regimens) ***Plus Consider*** Lorazepam 1-2 mg PO or SL before chemotherapy	Post-treatment: Oral corticosteroid (Dexamethasone 8 mg q24h for 3 days, or 4 days with cisplatin regimens) ***Plus*** Oral serotonin receptor antagonist (Ondansetron 8 mg q12h for 3 doses; OR Granisetron 1 mg q24h for 1 dose; OR Dolasetron 100 mg q24h for 1 dose) ***Or Plus*** Oral Metoclopramide (10-20 mg q4-6h for 2 to 3 days) ***Or Plus*** Dopamine receptor antagonist on an 'as needed' basis pre or post chemotherapy (Prochlorperazine 10 mg PO/PR q4-6h PRN)
High Emetic Risk: non-cisplatin	dacarbazine (DTIC) dactinomycin (Cosmegen) mechlorethamine (Mustargen) streptozotocin (Zanosar) hexamethylmelamine (Hexalen) carboplatin (Paraplatin) cyclophosphamide (Cytoxan) lomustine (CeeNU) carmustine (BiCNU) daunorubicin Cerubidine) doxorubicin (Adriamycin) epirubicin (Pharmorubicin) idarubicin (Idamycin) cytarabine (Cytosar) ifosfamide (Ifex) irinotecan (Camptosar)		

Notes:

- Serotonin receptor antagonist and dexamethasone given IV for higher doses of cisplatin; agents given PO for lower doses of cisplatin and other drugs.
- For multiple-day chemotherapy, give pre-treatment antiemetics each day of chemotherapy (plus one dose of Ondansetron qHS), begin post-treatment antiemetics after last dose of chemotherapy.
- Consider Aprepitant (125 mg IV prechemo & 80 mg IV q24h Days 2 & 3) when commercially-available in Canada.

Table 4.1. Chemotherapy-Induced Emesis: Emetic Risk Categories for Chemotherapeutic Agents and Guidelines (continued)

Acute Emetic Category	Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis
Intermediate Emetic Risk:	mitoxantrone (Novantrone) paclitaxel (Taxol) docetaxel (Taxotere) mitomycin (Mutamycin) topotecan (Hycamtin) gemcitabine (Gemzar) etoposide (Vepesid) teniposide (Vumon)	Pretreatment: Corticosteroid (oral Dexamethasone 4-8 mg before each dose of chemotherapy)	Post-treatment: No regular preventive use of antiemetics for delayed emesis May give a dopamine receptor antagonist on an 'as needed' basis pre or post chemotherapy (Prochlorperazine 10 mg PO/PR q4-6h PRN; OR Metoclopramide 10-20 mg PO q4-6h PRN)
		Note: Individual patients may require treatment similar to that recommended for high emetic risk agents. Combinations of agents in this class are not well studied, but they may occasionally cause more emesis for some patients, requiring treatment similar to that recommended for high-emetic-risk agents.	
Low Emetic Risk:	vinorelbine (Navelbine) fluorouracil methotrexate thioguanine (Lanvis) mercaptopurine (Purinethol) bleomycin (Blenoxane) asparaginase (Elspar) vindesine (Eldisine) vinblastine (Velban) vincristine (Oncovin) busulphan (Myleran) chlorambucil (Leukeran) melphalan (Alkeran) hydroxyurea (Hydrea) fludarabine (Fludara) cladribine (Leustatin) tamoxifen (Nolvadex)	Pretreatment: No routine pretreatment anti-emetics	Post-treatment: No regular preventive use of antiemetics for delayed emesis
		Note: Individual patients may require treatment similar to that recommended for intermediate-emetic-risk agents. Combinations of agents in this class are not well studied, but they may occasionally cause more emesis for some patients, requiring treatment similar to that recommended for intermediate-emetic-risk agents.	

4.3 Management of Anticipatory Chemotherapy-Induced Emesis

Anticipatory or conditioned emesis may occur in patients who have had poor control of either acute or delayed emesis with prior chemotherapy. Some factors that predispose patients to anticipatory emesis have been identified, including a history of motion sickness.

4.3.1. Prevention

Prevention of chemotherapy-induced emesis is seen as the best strategy for preventing anticipatory emesis. The most effective method to prevent anticipatory emesis is to use the effective antiemetic regimens for acute or delayed emesis.

4.3.2. Treatment

If anticipatory emesis occurs, behavioral therapy with systematic desensitization is an effective treatment. At the QEII HSC, a referral to the clinical psychologist or oncology nurse specialist is suggested, to access treatment services (including behavioural therapy) for anticipatory emesis.

4.4 Management of Nausea and Emesis in Pediatric Oncology

Guidelines for management of nausea and vomiting in pediatric cancer patients have been developed by the IWK Health Centre, and are available from this agency. The guidelines for pediatric oncology patients employs a wider range of emetogenicity, than the simpler system used for practical management of adult patients. This system ranks each chemotherapy agent (or agents above or below a dosing threshold) into 1 of 5 ranks, from 0 to 4. A chemotherapy regimen is assessed for emetogenicity by the highest ranked agent (similar to the adult method), then adjusted up by one level for each additional agent with a rank of 1 or more (up to a maximum rank = 5). The ranking of individual chemotherapy agents and antiemetic recommendations (for single-agent or combination regimens) are listed in Table 4.2. Note that ondansetron doses are rounded to the nearest 4mg or 8mg dose for the ODT formulation of tablets, or rounded to the nearest mL for the liquid formulation. Doses may be rounded down for chemotherapy with $\leq$ rank 2 or rounded up for > rank 2 chemotherapy.

4.5 Management of Emesis with High-Dose Chemotherapy

A serotonin receptor antagonist combined with a corticosteroid is suggested. For example, at the QEII HSC Bone Marrow Transplantation Program, the usual initial antiemetic treatment is ondansetron 8 mg IV q12h during all chemotherapy days, and dexamethasone 20 mg IV daily (before each chemotherapy dose).

4.6 Management of Chemotherapy-Induced Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles

Despite the use of optimal antiemetic therapy, a proportion of patients are expected to fail emetic control. 30% of patients receiving highly-emetogenic chemotherapy are likely to experience acute emesis despite appropriate antiemetic therapy, and up to 50% of these patients may experience delayed emesis.

Table 4.2 - Antiemetic Treatment for Pediatric Patients

Acute Emetogenic Potential of Individual Antineoplastic Agents

VERY HIGH Rank: 4
carmustine >250 mg/m²
cisplatin ≥ 50 mg/m²[a]
cyclophosphamide[a] > 1500 mg/m²
dacarbazine
mechlorethamine

HIGH Rank: 3
carboplatin[a]
carmustine ≤ 250 mg/m²
cisplatin[a] < 50 mg/m²[a]
cyclophosphamide[a] ≤ 1500 mg/m²
cytarabine > 1000 mg/m²
dactinomycin
daunorubicin > 60 mg/m²
doxorubicin > 60 mg/m²
methotrexate > 1000 mg/m²

MODERATE Rank: 2
cyclophosphamide[a] ≤ 750 mg/m²
daunorubicin ≤ 60 mg/m²
doxorubicin ≤ 60 mg/m²
epirubicin ≤ 90 mg/m²
etoposide ≥ 60 mg/m²

MODERATE (continued)
idarubicin
ifosfamide
methotrexate = 250-1000 mg/m²
mitoxantrone < 15 mg/m²
Radiotherapy to abdomen, mantle, cranium, cranial spine

MILD Rank: 1
etoposide < 60 mg/m²
methotrexate 51-249 mg/m²
procarbazine
teniposide

NONE Rank: 0
asparaginase
bleomycin
busulfan
chlorambucil
cytarabine < 1000 mg/m²
hydroxyurea
lomustine
mercaptopurine
methotrexate ≤ 50 mg/m²
thioguanine
vinblastine
vincristine

Initial Antiemetic Treatment Based upon Emetogenic Potential of Regimen

Emetogenic Rank of Regimen	Treatment Recommendations
VERY HIGH[b] (Rank > 4)	ondansetron 0.15-0.2 mg/kg (max 8 mg) IV/PO[c] pre-chemo and q6h PLUS metoclopramide 1 mg/kg (max 50 mg) IV, AND diphenhydramine 1 mg/kg (max 50 mg) IV – both q6h *(alternate ondansetron/ metoclopramide to give antiemetic q3h)* PRN dimenhydrinate 1 mg/kg (max 50 mg) IV/PO[c] q4h PRN PRN dexamethasone[a] 8 mg/m² (max 20mg/dose) IV q12-24h starting 24 hours post chemo PRN if nausea/ vomiting uncontrolled
HIGH[b] (Rank = 3)	ondansetron 0.15 mg/kg (max 8 mg) IV/ PO[c] pre-chemo and q8h PRN dimenhydrinate 1 mg/kg (max 50 mg) IV/PO[c] q4h PRN
MODERATE[b] (Rank = 2)	ondansetron 0.15 mg/kg (max 8 mg) IV/ PO[c] pre-chemo and q12h
MILD (Rank = 1)	ondansetron 0.1 mg/kg (max 8 mg) IV/PO[c] x 1 dose pre-chemo
NONE (Rank = 0)	No routine treatment

Table 4.2 - Antiemetic Treatment for Pediatric Patients (continued)

Management of Antiemetic Failure

Antiemetic Failure	Recommendation
Breakthrough Nausea/ Vomiting[e]	lorazepam 0.025-0.05 mg/kg/dose (max 4 mg/dose) IV/ PO/SL q6h PRN OR dimenhydrinate 1 mg/kg/dose IV/PO q4h PRN AND increase ondansetron dosing frequency (e.g. from q8h to q6h)[f] AND add dexamethasone[d], if appropriate AND modify antiemetic regimen for next cycle of chemotherapy (i.e. increase to next rank up for regimens < rank 4)
Anticipatory Nausea/ Vomiting	lorazepam (5-10 yrs: 0.5 mg/dose; > 10 yrs: 1 mg/dose) PO/SL qHS the night before chemo and/or the morning of chemo AND modify antiemetic regimen for next cycle of chemotherapy (i.e. increase to next rank up for regimens < rank 4)

Notes:

a) May also cause delayed or prolonged nausea and vomiting.
b) Regular antiemetics given 'round-the-clock' for twice the number of chemotherapy days, up to a duration of +3 days after chemotherapy. PRN antiemetics may be continued beyond this time.
c) Antiemetics given orally when appropriate. Oral ondansetron rounded to nearest dose of 4mg or 8mg.
d) Dexamethasone as an antiemetic may be contraindicated in some protocols or in patients receiving treatment for brain tumours.
e) Breakthrough occurs when the patient experiences > 2 vomits or retches within a 24 hour period, or experiences ≥ 3 hours of significant nausea per day, affecting the level of patient activity.
f) If patient fails on two consecutive cycles with ondansetron, substitute granisetron for ondansetron.

Adapted from IWK Guidelines

Nausea and vomiting should be assessed at each visit (or each inpatient day), for both current status and the patient's experience after the last chemotherapy treatment. Using the Common Toxicity Criteria (Table 3.1), a grade of 1 or more for vomiting or 2 or more for nausea are considered unacceptable toxicity. The patient should also be asked if the nausea or vomiting are tolerable, or if there are other reasons why the patient is nauseated. Patients with an unacceptable level of nausea or vomiting should be re-assessed for treatment and control strategies.

Strategies for alteration of the antiemetic therapies vary widely. Changes must be tailored to individual patients' needs and experiences. There are a variety of choices, which may be considered for individual patients. In consultation with each patient, additions or changes to the antiemetic treatment may be made. Each change should continue to be assessed for effectiveness, and altered again, if necessary and agreed by the

patient. For inadequately controlled acute nausea and/or vomiting, alternate management options may include:

1. Conduct a careful evaluation of emetic risk, considering antiemetic treatment, patient compliance with the antiemetic agents, emetogenicity of the chemotherapy, tumour factors, concurrent diseases which might contribute to nausea and vomiting, and other potentially emetogenic medications.
2. Determine that the best regimen is being given for the emetic setting (if not, consider changing to the optimal regimen).
3. Consider adding an antianxiety agent (eg. Lorazepam PO or SL) to the regimen.
4. If oral agents were used for the initial antiemetic treatment, consider changing to parenteral dosage of the same drugs and doses.
5. Consider adding a dopamine receptor antagonist (eg. Metoclopramide) to the serotonin receptor antagonist.
6. Consider substituting alternate agents from within pharmacologic class (eg. Granisetron or Dolasetron for Ondansetron; or Domperidone for Metoclopramide).
7. Consider substituting a dopamine receptor antagonist such as high-dose Metoclopramide for the serotonin receptor antagonist.
8. If available, and not used previously, consider addition of a Neurokinin-1 Receptor antagonist (e.g. Aprepitant).

For delayed nausea and/or vomiting, which is not adequately controlled, some additional or alternate options may include:

1. Consider adding additional agents to delayed antiemetics (eg. add PRN dopamine receptor antagonist or antianxiety agent, such as Lorazepam).
2. Consider adding non-pharmacologic treatment to drug therapy (eg., muscle relaxation, distraction, music therapy).
3. If available, and not used previously, consider addition of a Neurokinin-1 Receptor antagonist (e.g. Aprepitant).
4. Consider substituting alternate agents from within pharmacologic class (eg. Granisetron or Dolasetron for Ondansetron; or Domperidone for Metoclopramide).
5. Consider substituting serotonin receptor antagonist for dopamine receptor antagonist (eg. Ondansetron for Metoclopramide – re-assess antiemetic effectiveness with each cycle before re-ordering).
6. If available, and not used previously, consider addition of a Neurokinin-1 Receptor antagonist (e.g. Aprepitant).

4.7 Management of Radiotherapy-Induced Nausea and Vomiting

4.7.1. Risk Factors for Radiotherapy-Induced Nausea and Vomiting

The risk of emesis with radiotherapy varies with the treatment administered. Only a minority of patients receive radiation therapy of high emetic potential, and in that group of patients, the problem can be difficult to prevent or manage. As with chemotherapy-induced emesis, it is the identification of these risk groups that indicates whether antiemetic therapy should be given routinely on a preventative basis or

whether antiemetics should be reserved for treatment as needed by individual patients. The radiation oncology literature indicates that treatment field is one of the major determinants of emetic risk. More difficult to define, but also important considerations for risk, are the dose of radiotherapy administered per fraction and the pattern of fractionation.

4.7.2. Guidelines for Radiotherapy-Induced Nausea and Vomiting

Definition of Terms
Similar to the management of chemotherapy-induced emesis, management of radiotherapy-induced nausea and vomiting is based upon risk. The highest-risk group includes patients treated with total body irradiation. The intermediate risk group includes patients who receive hemibody irradiation, upper abdomen, abdominal-pelvic, mantle, nasopharyngeal, craniospinal irradiation, and cranial radiosurgery. The low risk group includes patients who receive radiation of the cranium only, breast, head and neck (other than nasopharyngeal), extremities, pelvis, and thorax.

Recommended antiemetic treatments for each risk category are outlined in Table 4.7.

4.8 Management of Nausea and Vomiting Induced by Other Drugs Used in Cancer Treatment

4.8.1. Opioids for Cancer Pain

It is a reasonable option to offer antiemetic treatment on an as-needed basis when opioids are started or doses are changed. A dopamine receptor antagonist (e.g. Prochlorperazine PO/SC, Haloperidol PO/SC, Metoclopramide PO/SC, Domperidone PO) may be considered as antiemetic treatment during opioid therapy. If emesis or nausea persists beyond a few days, antiemetics may be given on a regular basis. A regular laxative regimen should always be included with the opioid therapy, as prevention of constipation. Opioid-induced constipation will contribute towards the nausea and vomiting.

4.8.2. Other Emetogenic Drugs

Other drugs may induce nausea and vomiting, or contribute to existing problems with these symptoms. Some of these drugs include:

- Non-steroidal anti-inflammatory agents
- Antibiotics
- Iron supplements
- Alcohol
- Anticonvulsants
- Digoxin
- Withdrawal from opiates, benzodiazepines or SSRI antidepressants

When assessing a patient with nausea and/or vomiting, a complete medication history should always be included, with consideration of other medications which could be contributing factors. In patients with advanced cancer, one should question the need for continued use of emetogenic drugs (prescribed for other purposes) versus the adverse effects caused by these agents.

4.9 Non-Pharmacological Management of Nausea and Vomiting

4.9.1 Nutritional Support

A nutritional plan should be considered along with pharmacologic approaches for the prevention of nausea and vomiting due to cancer treatment or disease. Patients may be assessed by a clinical dietitian if appropriate. Simple patient education on nutritional methods may be offered by different health care professionals, and may include appropriate helpful hints to assist patients (listed in Appendix VI).

Patients who experience nausea may require additional strategies beyond the preventative nutritional plan. Assessment and suggested interventions by a clinical dietitian is encouraged, where available.

Patients who experience uncontrolled vomiting require more aggressive nutritional management, including fluid replacement. Assessment and monitoring by a clinical dietitian is recommended. Alternative nutritional support, such as peripheral parenteral nutrition (PPN) of central total parenteral nutrition (TPN) may be necessary.

4.9.2 Management of Nausea and Vomiting with Natural Products

Natural products, including ginger or chamomile, may be considered for the management of nausea and vomiting as adjuncts to appropriate pharmacologic agents and other methods. Like other pharmacologic agents, natural products may also cause adverse effects (e.g. increased bleeding with ginger), which should be considered.

4.9.3 Non-Pharmacologic Management of Nausea and Vomiting

Non-pharmacological management of nausea and vomiting may improve control of emesis events, or the perception of event control. The active patient participation, required for non-pharmacological management, may give the patient a greater sense of control and empowerment and patients may be more positive toward their chemotherapy experience.

Muscle relaxation techniques, distraction and music therapy can be efficacacious non-pharmacological strategies. Environmental conditions may influence nausea and vomiting. Interventions such as a pleasant, quiet room with fresh air, a place to rest comfortably, and a change of position can all have positive effects on nausea and vomiting. An environment free of strong or unpleasant odours is helpful. Fatigue may also influence nausea and vomiting.

Part 5. Practice Pathways

Management of chemotherapy-induced nausea and vomiting includes treatment strategies for both acute (within 24 hours of chemotherapy administration) and delayed (>24 hours after chemotherapy) emesis.

To plan the initial antiemetic treatment for adult cancer patients, the clinician should assess the chemotherapy regimen to be given (Assessment tools- Page 2). Based on the chemotherapy agent with the highest potential to cause nausea and vomiting (emetogenic potential), appropriate antiemetic agents are selected to manage the acute emesis and delayed emesis (see Page 4 for Adults or Page 6 for Pediatric Patients). These are prescribed along with the chemotherapy. Some new agents pending approval in Canada, with superior antiemetic management outcomes, are included in the options for consideration.

Some agents may be ordered as take-home prescriptions, for dispensing by the patient's community pharmacy. Clinicians must keep in mind the costs of these prescription medications and the patient's ability to pay for these drugs (including co-payments of prescription insurance and uninsured patients).

With each cycle of chemotherapy, nausea and vomiting are assessed, using the Common Toxicity Criteria (or the Graphic Rating Scale) for screening and outcome assessment (see Page 8). Attention must focus on both the present circumstances (i.e. how the patient feels right now) and the historic experience since the last chemotherapy treatment (i.e. worst feelings or emesis after the last treatment). If a patient has experienced an unacceptable level of nausea (>2) or vomiting (>1), and this experience has not been influenced by some other causal factor, the antiemetic prevention strategy should be reconsidered, and, if necessary, altered (see Ongoing Antiemetic Treatment for adults- page 5).

Effective management of acute and delayed nausea and vomiting is crucial to prevention of anticipatory nausea and vomiting. In addition to pharmacologic antiemetic agents, other drugs (such as benzodiazepines) and non-pharmacologic methods (such as muscle relaxation, distraction or music therapy) can modify the patient experience and reduce morbidity and anxiety from nausea and vomiting experiences(s).

Cancer patients may also experience chronic nausea or vomiting not related to treatment. Careful assessment for reversible underlying causes, and a simple regimen of gastric promotility agents are reasonable steps to deal with this common problem. A step-wise approach is outlined on page 8.

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. However, guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision. A full-text version of this guideline is also available. Both versions of this guideline will be revised, from time to time, as new evidence becomes available. Current versions of this guideline are available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

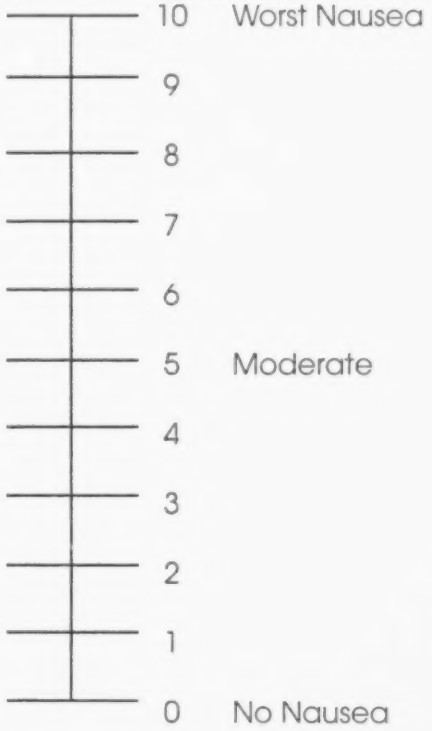
Assessment of Nausea and Vomiting

Assessment Recommendations for Nausea and Vomiting	
Chemotherapy treatment phase	• CTC at each treatment visit, or weekly for continuous treatment; include subjective comments on patient experience • Inpatients: assess with CTC before each chemotherapy administration or daily for continuous treatment; repeat CTC 24 hours after treatment and continue q24h for delayed or chronic N&V • If symptomatic, assess q4h until symptoms resolve
Radiotherapy treatment phase	• CTC weekly or at review clinic visit
Follow-up after active treatment phase	• CTC at scheduled follow-up visits immediately after active treatment phase, if nausea or vomiting were problematic during active treatment; follow until symptoms resolved

Symptom of cancer (usually advanced)	• CTC at each visit if symptomatic with nausea or vomiting; may assess and follow as required by severity of symptoms
	• Detailed physical history and physical examination at start and repeated at each visit
	  • If patient admitted to hospital, assess with CTC daily until symptoms resolved
	  • If patient cannot use CTC, consider using Graphic Rating Scale

Common Toxicity Criteria (CTC)	
Grade	**Nausea**
0	none
1	loss of appetite without alteration in eating habits
2	oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs
3	inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 hrs
4	Life-threatening consequences
	Vomiting
0	none
1	1 episode in 24 hours; IV fluids indicated <24 hrs
2	2-5 episodes in 24 hours
3	≥6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24 hrs
4	Life-threatening consequences

Graphic Rating Scale for Nausea



Antiemetic Agents for Management of Treatment-Induced Nausea and Vomiting

Pre-Chemotherapy Drugs & Doses- High-Risk Chemotherapy

Serotonin (5HT3) Receptor Antagonist

- Ondansetron (Zofran) 8 mg PO or IV
  OR
- Granisetron (Kytril) 2 mg PO or 1 mg IV
  OR
- Dolasetron (Anzemet) 100-200 mg PO or 100 mg IV
  PLUS

Corticosteroid

- Dexamethasone (Decadron) 8-20 mg PO or IV
  (Higher doses for highly emetogenic chemo)
  All doses given 15-30 minutes prior to chemotherapy

Intermediate-Risk Chemotherapy

Corticosteroid

- Dexamethasone 4-8 mg PO, once before chemotherapy
  AND/OR

Dopamine Receptor Antagonist

- Metoclopramide (Maxeran) 10-20 mg PO before chemotherapy
  OR
- Prochlorperazine (Stemetil) 10 mg PO before chemotherapy

Other Drugs and Doses to Consider- Neurokinin-1 (NK1) Receptor Antagonist

Aprepitant (Emend) 125 mg PO pre-chemo
Aprepitant (Emend) 80 mg PO once daily on Days 2 & 3
Notes:

- Not currently available in Canada
- If NK1 Receptor antagonist given, Serotonon RA or Dopamine RA would not be needed for delayed emesis prevention

Post-Chemotherapy Drugs & Doses- High-Risk Chemotherapy

Corticosteroid

- Dexamethasone 8 mg PO once or twice daily for 2 to 3 days (3-4 days with cisplatin)
  PLUS

Serotonin Receptor Antagonist or Dopamine Receptor Antagonist

- Ondansetron 8 mg PO q12h for 3 doses
- (Granisetron or Dolasetron effective with only pre-chemo dose, but may be given q24h for one dose)
  OR
- Metoclopramide 10-20 mg PO 2 to 4 times per day for 2 to 3 days (3-4 days with cisplatin)
- May add Diphenhydramine (Benadryl) 25-50 mg PO, to prevent extrapyramidal reactions
  OR
- Prochlorperazine 10mg PO q4-6h PRN

Intermediate-Risk Chemotherapy

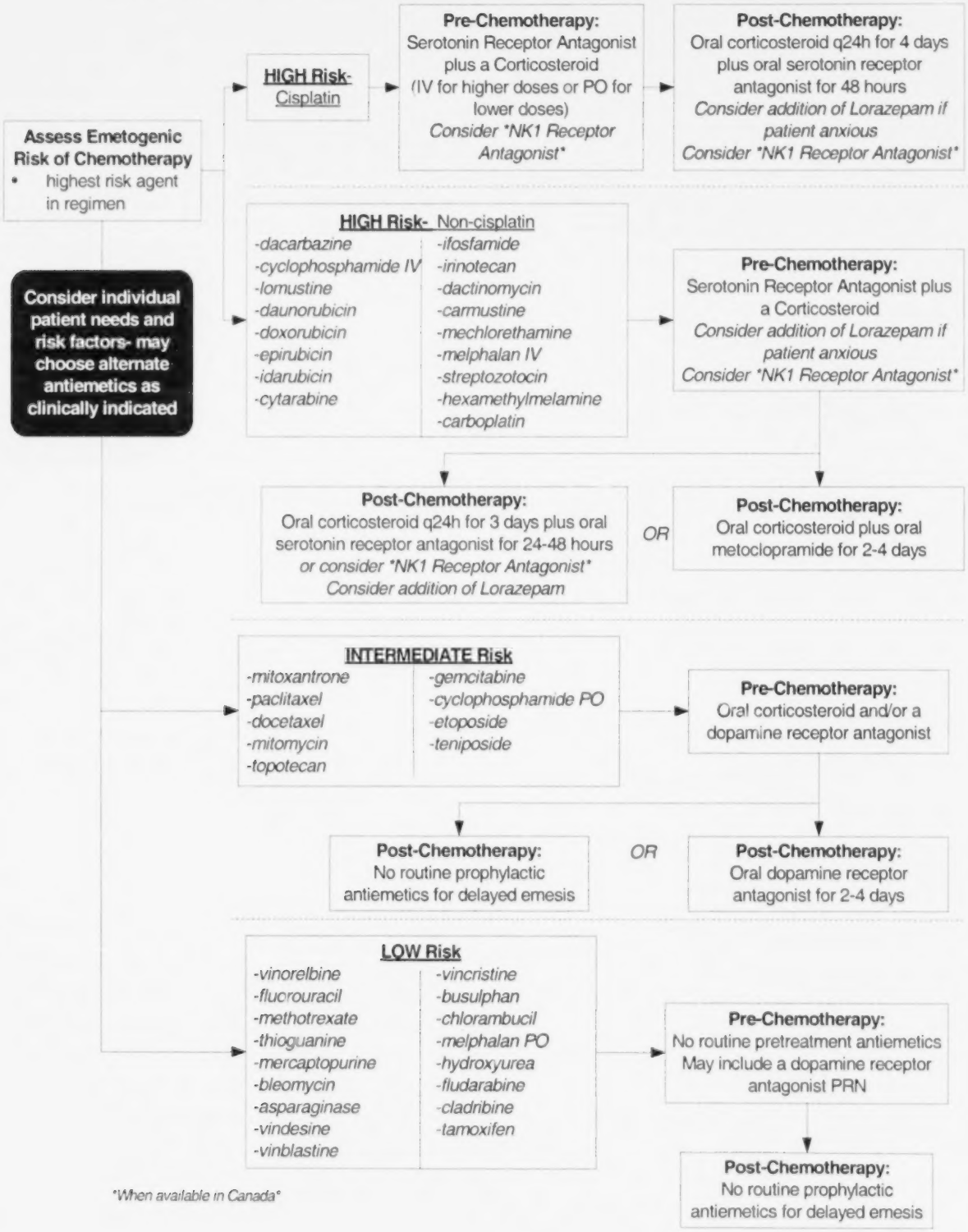
- Prochlorperazine 10 mg PO q4-6h PRN
- Metoclopramide 10 mg PO q4h PRN

Adjuvant Drugs and Doses

(May add to other antiemetic regimens)

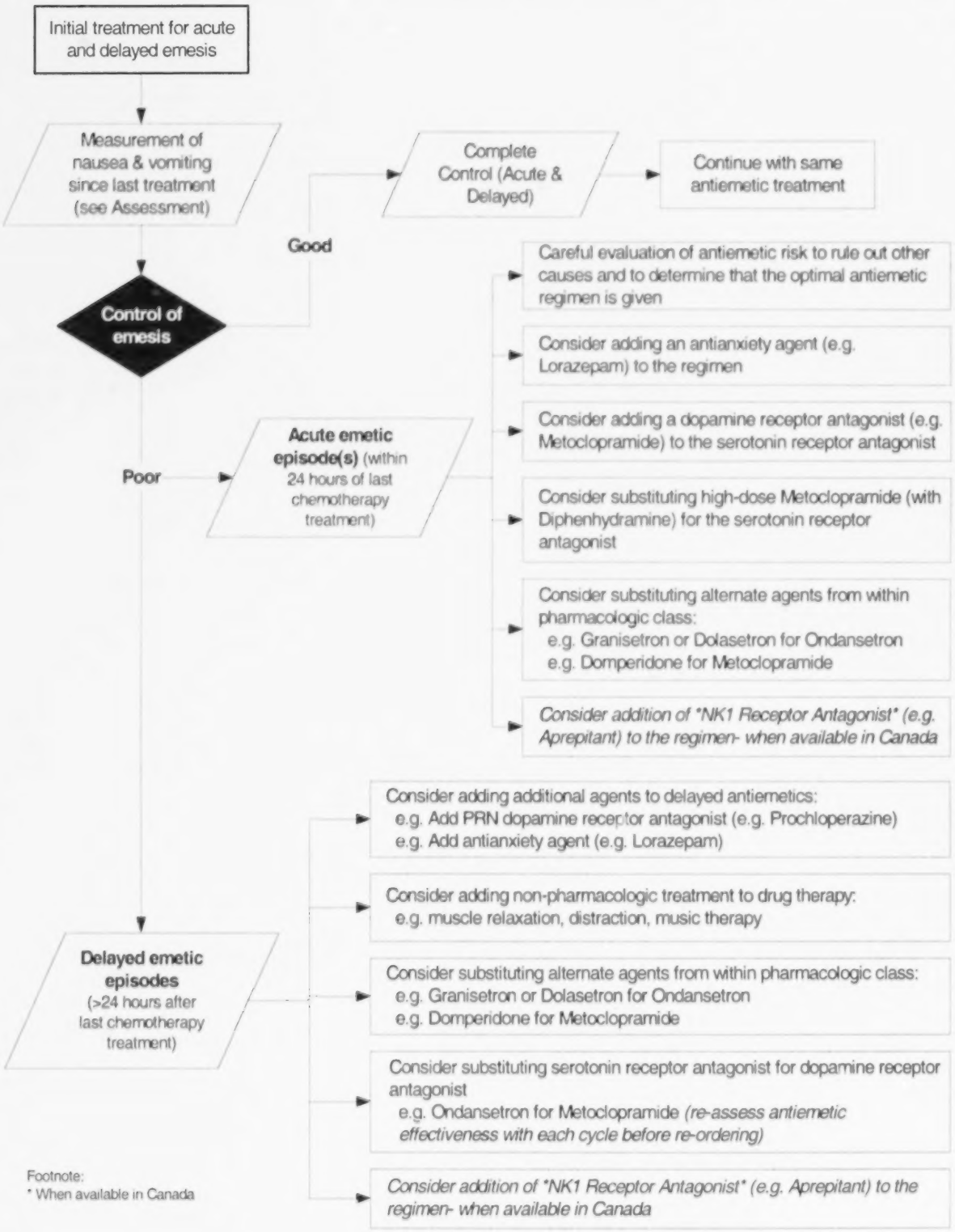
- Lorazepam (Ativan) 1-2 mg PO or SL before chemotherapy
- Dronabinol (Marinol) 2.5-10 mg q4-12h OR Nabilone (Cesamet) 1-2 mg PO BID- for selected patients only

Initial Antiemetic Treatment for Adult Chemotherapy Patients



When available in Canada

Ongoing Antiemetic Treatment for Adult Chemotherapy Patients


Initial treatment for acute and delayed emesis
Measurement of nausea & vomiting since last treatment (see Assessment)
Complete Control (Acute & Delayed)
Continue with same antiemetic treatment
Good
Control of emesis
Careful evaluation of antiemetic risk to rule out other causes and to determine that the optimal antiemetic regimen is given
Consider adding an antianxiety agent (e.g. Lorazepam) to the regimen
Consider adding a dopamine receptor antagonist (e.g. Metoclopramide) to the serotonin receptor antagonist
Poor
Acute emetic episode(s) (within 24 hours of last chemotherapy treatment)
Consider substituting high-dose Metoclopramide (with Diphenhydramine) for the serotonin receptor antagonist
Consider substituting alternate agents from within pharmacologic class:
e.g. Granisetron or Dolasetron for Ondansetron
e.g. Domperidone for Metoclopramide
Consider addition of *NK1 Receptor Antagonist* (e.g. Aprepitant) to the regimen- when available in Canada
Consider adding additional agents to delayed antiemetics:
e.g. Add PRN dopamine receptor antagonist (e.g. Prochloperazine)
e.g. Add antianxiety agent (e.g. Lorazepam)
Consider adding non-pharmacologic treatment to drug therapy:
e.g. muscle relaxation, distraction, music therapy
Delayed emetic episodes (>24 hours after last chemotherapy treatment)
Consider substituting alternate agents from within pharmacologic class:
e.g. Granisetron or Dolasetron for Ondansetron
e.g. Domperidone for Metoclopramide
Consider substituting serotonin receptor antagonist for dopamine receptor antagonist
e.g. Ondansetron for Metoclopramide (re-assess antiemetic effectiveness with each cycle before re-ordering)
Consider addition of *NK1 Receptor Antagonist* (e.g. Aprepitant) to the regimen- when available in Canada

Footnote:
* When available in Canada

Management of Nausea and Vomiting - Pediatric Cancer Patients

VERY HIGH **Rank: 4**
carmustine >250 mg/m²
cisplatin ≥ 50 mg/m² *
cyclophosphamide > 1500 mg/m² *
dacarbazine
mechlorethamine

HIGH **Rank: 3**
carboplatin *
carmustine ≤ 250 mg/m²
cisplatin < 50 mg/m² *
cyclophosphamide *
> 750 mg/m² and ≤ 1500 mg/m²
cytarabine > 1000 mg/m²
dactinomycin
daunorubicin > 60 mg/m²
doxorubicin > 60 mg/m²
methotrexate > 1000 mg/m²

MODERATE **Rank: 2**
cyclophosphamide ≤ 750 mg/m² *
daunorubicin ≤ 60 mg/m²
doxorubicin ≤ 60 mg/m²
epirubicin ≤ 90 mg/m²
etoposide ≥ 60 mg/m²
idarubicin
ifosfamide
methotrexate = 250-1000 mg/m²
mitoxantrone < 15 mg/m²
Radiotherapy to abdomen, mantle, cranium, cranial spine

MILD **Rank: 1**
etoposide < 60 mg/m²
methotrexate 51-249 mg/m²
procarbazine
teniposide

NONE **Rank: 0**
asparaginase
bleomycin
busulfan
chlorambucil
cytarabine < 1000 mg/m²
hydroxyurea
lomustine
mercaptopurine
methotrexate ≤ 50 mg/m²
thioguanine
vinblastine
vincristine

Management of chemotherapy-induced nausea and vomiting in children differs from adults. Children are much more sensitive to acute dystonic reactions from dopamine receptor antagonists and are more likely to develop anticipatory nausea and vomiting. The system to rank emetogenicity of drugs and regimens includes additional gradations, to identify patients who are in greater need of higher dose antiemetics and dopamine receptor antagonists. The emetogenicity ranking of full regimens is outlined on this page, and the pediatric dosing is on the following page. Antiemetic agents for children with cancer may be given in the hospital or filled at a community pharmacy. Specific directions for antiemetic treatment will be given by the pediatric oncology program.

Regimen Emetogenicity Rank

1. Start with the highest ranked individual drug
2. For every other drug to be given at the same time, and with a rank >0, add 1 rank per drug to equal the drug rank for the total regimen. (maximum rank of 5)

REGIMEN EMETOGENICITY RANK

See "**Antiemetic Treatment for Pediatric Cancer Patients**" next page

* may also cause delayed or prolonged nausea and vomiting

Antiemetic Treatment for Pediatric Cancer Patients

REGIMEN EMETOGENICITY RANK

Very High[a] Rank ≥ 4

ondansetron 0.15-0.2 mg/kg (max 8 mg) IV/PO pre-chemo and q6h[b]

AND

metoclopramide 1 mg/kg (max 50 mg) IV q6h

WITH

diphenhydramine 1 mg/kg (max 50 mg) IV q6h

Alternate ondansetron/metoclopramide to give antiemetic q3h

***PLUS** (as needed)*

dimenhydrinate 1 mg/kg (max 50 mg) IV/PO q4h PRN[b]

AND/OR

dexamethasone 8 mg/m2 (max 20mg/dose) IV q12-24h starting 24 hours post chemo PRN if nausea/vomiting uncontrolled[c]

High[a] Rank = 3

ondansetron 0.15 mg/kg (max 8 mg) IV/PO pre-chemo and q8h[b]

***PLUS** (as needed)*

dimenhydrinate 1 mg/kg (max 50 mg) IV/PO q4h PRN[b]

Moderate[a] Rank = 2

ondansetron 0.15 mg/kg (max 8 mg) IV/PO pre-chemo and q12h[b]

Mild Rank = 1

ondansetron 0.1 mg/kg (max 8 mg) IV/PO x 1 dose pre-chemo[b]

None Rank = 0

No routine treatment

Anticipatory Nausea/Vomiting

lorazepam (5-10 yrs: 0.5 mg/dose; > 10 yrs: 1 mg/dose) PO/SL qHS the night before chemo and/or the morning of chemo

AND

modify antiemetic regimen for next cycle of chemotherapy (i.e. increase to next rank up for regimens < rank 4)

lorazepam 0.025-0.05 mg/kg/dose (max 4 mg/dose) IV/PO/SL q6h PRN

OR

dimenhydrinate 1 mg/kg/dose IV/PO q4h PRN[b]

AND

increase ondansetron dosing frequency (e.g. from q8h to q6h)[e]

AND

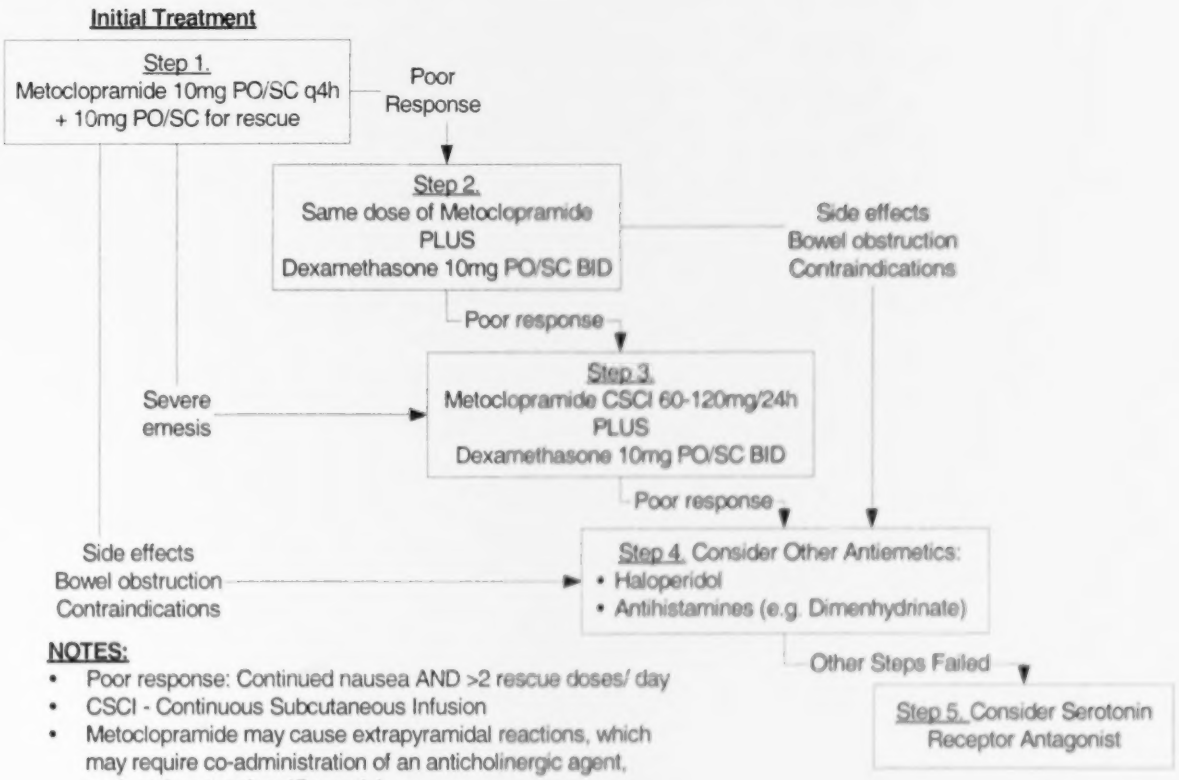
add dexamethasone, if appropriate[c]

AND

modify antiemetic regimen for next cycle of chemotherapy (i.e. increase to next rank up for regimens < rank 4)

a. Regular antiemetics given 'round-the-clock' for twice the number of chemotherapy days, up to a duration of +3 days after chemotherapy. PRN antiemetics may be continued beyond this time.
b. Antiemetics given orally when appropriate. Oral Ondansetron rounded to nearest dose of 4mg or 8mg tablet or appropriate dose of liquid
c. Dexamethasone as an antiemetic may be contraindicated in some protocols or in patients receiving treatment for brain tumours.
d. Breakthrough occurs when the patient experiences > 2 vomits or retches within a 24 hour period, or experiences ≥ 3 hours of significant nausea per day, affecting the level of patient activity.
e. If patient fails on 2 consecutive cycles with ondansetron, substitute granisetron for ondansetron.

Antiemetic Treatment for Chronic Nausea



NOTES:

- Poor response: Continued nausea AND >2 rescue doses/ day
- CSCI - Continuous Subcutaneous Infusion
- Metoclopramide may cause extrapyramidal reactions, which may require co-administration of an anticholinergic agent, such as benztropine *(Cogentin)*

Antiemetic Treatment for Radiotherapy Patients

Radiotherapy is available only at a cancer centre. Antiemetic treatment will usually be determined by a radiation oncologist.

Assess Emetogenic Risk of Radiotherapy:
- risk by field size, location and dosage

ANTIEMETIC DRUGS AND DOSES

Serotonin Receptor Antagonists
- Ondansetron 8mg PO (may use ODT formulation) Q12H OR
- Granisetron 2mg PO OR
- Dolasetron 100-200mg PO

Dopamine Receptor Antagonists
- Prochlorperazine 10mg PO OR
- Metoclopramide 10-20mg PO

Corticosteroid
- Dexamethasone 4mg PO QD

HIGH Risk
Total Body Irradiation

→ **Daily before first fraction and 12 hours later (i.e. twice daily):**
- Serotonin receptor antagonist PLUS corticosteroid
- Dopamine receptor antagonist PRN only

INTERMEDIATE Risk
- Hemibody Irradiation
- Upper abdomen
- Abdominal-Pelvic
- Mantle
- Nasopharynx
- Cranium (radiosurgery)
- Craniospinal

→ **Before each fraction and 12 hours later (i.e. twice daily):**
- Serotonin receptor antagonist PLUS corticosteroid (and dopamine receptor antagonist PRN only); or
- Dopamine receptor antagonist +/- corticosteroid

LOW Risk
- Cranium only
- Breast
- Head and neck (other than nasopharynx)
- Extremities
- Pelvis
- Thorax

→ **As-needed basis:**
- Dopamine receptor antagonist, or
- Corticosteroid, or
- Serotonin receptor antgonist

1278 Tower Road
5th floor Bethune Building
Halifax, Nova Scotia B3H 2Y9

Phone: 902-473-4645
Toll free: 1-866-599-2267
Fax: 902-473-4631

Email: info@ccns.nshealth.ca
www.cancercare.ns.ca